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For : 2,3,6-TRISUBSTITUTED-4-PYRIMIDONE DERIVATIVES

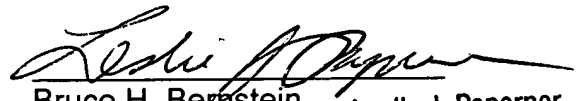
CLAIM OF PRIORITY

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Sir:

Applicant hereby claims the right of priority granted pursuant to 35 U.S.C. 119 and 365 based upon Japanese Application Nos. 2003-126021, filed March 26, 2003 and 2003-126022, filed March 26, 2003. The International Bureau already should have sent certified copies of the Japanese applications to the United States designated office. If the certified copies have not arrived, please contact the undersigned.

Respectfully submitted,
Kazutoshi WATANABE et al.


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26. 3. 2004

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This is to certify that the annexed is a true copy of the following application as filed with this Office.

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Date of Application:

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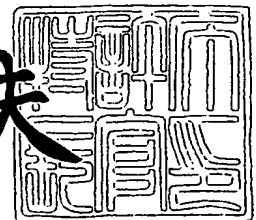
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特許庁長官
Commissioner,
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今 井 康 夫



【書類名】 特許願

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【特記事項】 特許法第36条の2第1項の規定による特許出願

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【手数料の表示】

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【その他】 サノフィーサンテラボはフランス国の法律に基づく法人

【提出物件の目録】

【物件名】 外国語明細書 1

【物件名】 外国語要約書 1

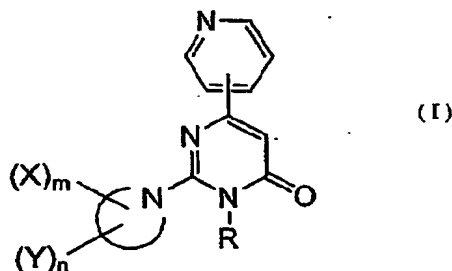
【書類名】 外国語明細書

1. TITLE OF INVENTION

3-SUBSTITUTED-4-PYRIMIDONE DERIVATIVES

2. CLAIMS

1. A pyrimidone derivative represented by formula (I) or a salt thereof, or a solvate thereof or a hydrate thereof:



wherein R represents a C₁-C₁₂ alkyl group which may be substituted;
the ring of:



represents piperazine ring or piperidine ring;

each X independently represents a C₁-C₈ alkyl group which may be substituted, an optionally partially hydrogenated C₆-C₁₀ aryl ring which may be substituted, an indan ring which may be substituted, an optionally substituted heterocyclic ring having 1 to 4 hetero atoms selected from the group consisting of oxygen atom, sulfur atom, and nitrogen atom, and having 5 to 10 ring-constituting atoms in total, a phenylamino group which may be substituted, or X¹-CO- wherein X¹ represents a C₆-C₁₀ aryl ring which may be substituted or a C₁-C₈ alkyl group which may be substituted;

m represents an integer of 1 to 3;

each Y independently represents a halogen atom, a hydroxy group, a cyano group, a C₁-C₈ alkyl group which may be substituted, Y¹-CO- wherein Y¹ represents a C₆-C₁₀ aryl ring which may be substituted or a C₁-C₈ alkyl group which may be substituted or Y²-O-CO- wherein Y² represents a C₁-C₈ alkyl group which may be substituted;

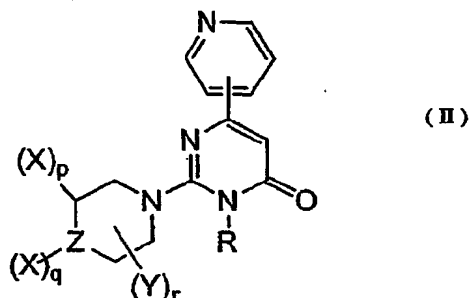
n represents an integer of 0 to 8;

when X and Y or two Y groups are attached on the same carbon atom, they may combine to each other to form a C₂-C₆ alkylene group;

and when m is 1, n is 0, and X is X¹-CO-,

- (1) X does not bind to 3-position of unsubstituted 1-piperazinyl group or does not bind to 3-position of a 4-alkyl-1-piperazinyl group; or
- (2) X does not bind to 3-position or 4-position of non-substituted 1-piperidinyl group.

2. The pyrimidone derivative or the salt thereof, or the solvate thereof or the hydrate thereof according to claim 1 having the following formula(II)



wherein R, X and Y are the same as those defined in claim 1;

p is 0 or 1; q is 0 or 1; r is an integer of 0 to 6; p+q is 1 or 2;

and Z represents N or CZ¹ wherein Z¹ represents hydrogen atom or Y.

3. The pyrimidone derivative or the salt thereof, or the solvate thereof or the hydrate thereof according to claim 2, wherein R is a C₁-C₈ alkyl group which may be substituted by a C₃-C₈ cycloalkyl group.

4. The pyrimidone derivative or the salt thereof, or the solvate thereof or the hydrate thereof according to claim 3, wherein R is methyl group or ethyl group; Y is in 3-, 4- or 5-position of the piperazine ring or the piperidine ring; p+q is 1; and r is an integer of 0 to 3.

5. The pyrimidone derivative or the salt thereof, or the solvate thereof or the hydrate thereof according to claim 4, wherein X is a C₁-C₈ alkyl group which may be substituted or a C₆-C₁₀ aryl ring which may be substituted; Y is a C₁-C₆ alkyl group which may be substituted; p is 1; q is 0; r is an integer of 0 to 3; and Z is N or

CH.

6. The pyrimidone derivative or the salt thereof, or the solvate thereof or the hydrate thereof according to claim 5, wherein X is a benzene ring which may be substituted, a benzyl group which may be substituted; Y is a methyl group which may be substituted; Z is N and r is 0 or 1.

7. The pyrimidone derivative or the salt thereof, or the solvate thereof or the hydrate thereof according to claim 4, wherein X is a benzene ring which may be substituted, a benzyl group which may be substituted, a benzoyl group which may be substituted, or a benzisothiazol ring which may be substituted; Y is a methyl group which may be substituted; Z is N and p is 0.

8. The pyrimidone derivative or the salt thereof, or the solvate thereof or the hydrate thereof according to claim 4, wherein X is a C₁-C₈ alkyl group substituted by a benzene ring which may be substituted or a benzene ring which may be substituted; Y is a hydroxy group, a cyano group, or Y¹-CO- wherein Y¹ is a C₁-C₈ alkyl group; Z is CH or C-Y and r is 0 or 1.

9. The pyrimidone derivative or the salt thereof, or the solvate thereof or the hydrate thereof according to claim 8, wherein X is a benzyl group which may be substituted or a benzene ring which may be substituted; Y is a hydroxy group, a cyano group, or an acetyl group; Z is CH or C-Y and r is 0 or 1.

10. A pyrimidone derivative which is selected from the group consisting of:
2-(3-Phenylpiperazin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
2-(3-(4-Fluorophenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
2-(3-(3-Fluorophenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
2-(3-(2-Fluorophenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
2-(3-(4-Chlorophenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
(S)-2-(3-(4-Chlorophenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
(R)-2-(3-(4-Chlorophenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
2-(3-(3-Chlorophenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
2-(3-(2-Chlorophenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
2-(3-(4-Bromophenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;

2-(3-(3-Bromophenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-pyrimidin-4-one;
2-(3-(2-Bromophenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-pyrimidin-4-one;
2-(3-(4-Methylphenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-pyrimidin-4-one;
2-(3-(3-Methylphenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-pyrimidin-4-one;
2-(3-(2-Methylphenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-pyrimidin-4-one;
2-(3-(4-Cyanophenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-pyrimidin-4-one;
2-(3-(3-Cyanophenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-pyrimidin-4-one;
2-(3-(2-Cyanophenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-pyrimidin-4-one;
2-(3-(4-Methoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-pyrimidin-4-one;
2-(3-(3-Methoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-pyrimidin-4-one;
2-(3-(2-Methoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-pyrimidin-4-one;
2-(3-(2-Ethoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-pyrimidin-4-one;
2-(3-(5-Fluoro-2-methoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-
pyrimidin-4-one;
2-(3-(4-Fluoro-3-methoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-
pyrimidin-4-one;
2-(3-(4-Fluoro-2-methoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-
pyrimidin-4-one;
(*S*)-2-(3-(4-Fluoro-2-methoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-
pyrimidin-4-one;
(*R*)-2-(3-(4-Fluoro-2-methoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-
pyrimidin-4-one;
2-(3-(4-Chloro-2-methoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-
pyrimidin-4-one;
2-(3-(4-Fluoro-2-methylphenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-
pyrimidin-4-one;
2-(3-(2-Fluoro-6-methoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-
pyrimidin-4-one;
2-(3-(5-Bromo-2-methoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-
pyrimidin-4-one;
2-(3-(2-Bromo-4-fluorophenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-
pyrimidin-4-one;
2-(3-(2-Chloro-6-fluorophenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-
pyrimidin-4-one;

2-(3-(2,4-Difluorophenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
2-(3-(2,6-Difluorophenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
2-(3-(2,6-Dichlorophenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
2-(3-(2,4-Dimethoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
2-(3-(3,4-Dimethoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
2-(3-(2,5-Dimethoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
2-(3-(2,6-Dimethoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
2-(3-(2,4-Difluoro-6-methoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;(1034)
2-(3-(5-Cyano-2-methoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
2-(3-(4-Cyano-2-methoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
2-(3-(1-Naphthyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
2-(3-(2-Naphthyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
2-(3-(2,3-Dihydrobenzofuran-7-yl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
2-(3-(Benzofuran-2-yl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
(S)-2-(3-(Benzofuran-2-yl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
2-(3-(4-(Pyrrolidin-1-yl-methyl)phenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
2-(3-(4-(Pyrrolidin-1-yl)phenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
2-(3-(2-methoxy-4-(pyrrolidin-1-yl)phenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
2-(3-(2-methoxy-5-(pyrrolidin-1-yl)phenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-

3H-pyrimidin-4-one;
2-(3-(4-(Phenyl)phenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
2-(3-(4-(4-Fluorophenyl)phenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
2-(3-(4-(4-Methoxyphenyl)phenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
2-(3-(4-(2-Methoxyphenyl)phenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
2-(3-(4-(Morpholin-4-yl)phenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
2-(3-(4-(4-Methylpiperazin-1-yl)phenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
2-(4-Phenylpiperazin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
2-(4-Benzylpiperazin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
2-(4-Benzoylpiperazin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
2-(4-(1,2-Benzisothiazol-3-yl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
2-(4-Methyl-3-phenylpiperazin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
2-(3-(4-Fluoro-2-methoxyphenyl)-4-methylpiperazin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
(S)-2-(3-(4-Fluoro-2-methoxyphenyl)-4-methylpiperazin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
(R)-2-(3-(4-Fluoro-2-methoxyphenyl)-4-methylpiperazin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
2-(4-Acetyl-3-(4-fluoro-2-methoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
2-(4-Benzyl-3-(4-fluoro-2-methoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
2-(4-Benzyl-3-(ethoxycarbonyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
2-(4-methyl-3-(1-naphthyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
2-(5,5-Dimethyl-3-(2-methoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;

2-(3-Phenylpiperidin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-pyrimidin-4-one;
2-(3-(4-Fluorophenyl)piperidin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-pyrimidin-4-one;
2-(3-(3-Fluorophenyl)piperidin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-pyrimidin-4-one;
2-(3-(2-Fluorophenyl)piperidin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-pyrimidin-4-one;
2-(3-(4-Chlorophenyl)piperidin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-pyrimidin-4-one;
2-(3-(4-Bromophenyl)piperidin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-pyrimidin-4-one;
2-(3-(4-Methoxyphenyl)piperidin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-pyrimidin-4-one;
2-(3-(3-Methoxyphenyl)piperidin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-pyrimidin-4-one;
2-(3-(2-Methoxyphenyl)piperidin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-pyrimidin-4-one;
2-(3-(4-((Pyrrolidin-1-yl)methyl)phenyl)piperidin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-pyrimidin-4-one;
(*S*)-2-(3-(4-(Pyrrolidin-1-yl-methyl)phenyl)piperidin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-pyrimidin-4-one;
(*R*)-2-(3-(4-(Pyrrolidin-1-yl-methyl)phenyl)piperidin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-pyrimidin-4-one; and
2-(3-Hydroxy-3-phenylpiperidin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-pyrimidin-4-one,
or a salt thereof, or a solvate thereof or a hydrate thereof.

11. A medicament comprising as an active ingredient a substance selected from the group consisting of the pyrimidone derivative represented by formula (I) and a salt thereof, and a solvate thereof and a hydrate thereof according to claim 1.

12. A tau protein kinase 1 inhibitor selected from the group consisting of the pyrimidone derivative represented by formula (I) and a salt thereof, and a solvate thereof and a hydrate thereof according to claim 1.

13. The medicament according to claim 11 which is used for preventive and/or therapeutic treatment of a disease caused by tau protein kinase 1 hyperactivity.

14. The medicament according to claim 11 which is used for preventive and/or therapeutic treatment of a neurodegenerative disease.

15. The medicament according to claim 14, wherein the neurodegenerative disease is selected from the group consisting of Alzheimer disease, ischemic cerebrovascular accidents, Down syndrome, cerebral bleeding due to cerebral amyloid angiopathy, progressive supranuclear palsy, subacute sclerosing panencephalitic parkinsonism, postencephalitic parkinsonism, pugilistic

encephalitis, Guam parkinsonism-dementia complex, Lewy body disease, Pick's disease, corticobasal degeneration, frontotemporal dementia, vascular dementia, traumatic injuries, brain and spinal cord trauma, peripheral neuropathies, retinopathies, and glaucoma.

16. The medicament according to claim 11, wherein the disease is selected from the group consisting of non-insulin dependent diabetes, obesity, manic depressive illness, schizophrenia, alopecia, breast cancer, non-small cell lung carcinoma, thyroid cancer, T or B-cell leukemia, and a virus-induced tumor.

3. DETAILED DESCRIPTION OF INVENTION

Technical Field

The present invention relates to compounds that are useful as an active ingredient of a medicament for preventive and/or therapeutic treatment of diseases mainly caused by abnormal activity of tau protein kinase 1, such as neurodegenerative diseases (e.g. Alzheimer disease).

Background Art

Alzheimer disease is progressive senile dementia, in which marked cerebral cortical atrophy is observed due to degeneration of nerve cells and decrease of nerve cell number. Pathologically, numerous senile plaques and neurofibrillary tangles are observed in brain. The number of patients has been increased with the increment of aged population, and the disease arises a serious social problem. Although various theories have been proposed, a cause of the disease has not yet been elucidated. Early resolution of the cause has been desired.

It has been known that the degree of appearance of two characteristic pathological changes of Alzheimer disease well correlates to the degree of intellectual dysfunction. Therefore, researches have been conducted from early 1980's to reveal the cause of the disease through molecular level investigations of components of the two pathological changes. Senile plaques accumulate extracellularly, and β amyloid protein has been elucidated as their main component (abbreviated as "A β " hereinafter in the specification: Biochem. Biophys. Res. Commun., 120, 855 (1984); EMBO J., 4, 2757 (1985); Proc. Natl. Acad. Sci. USA,

82, 4245 (1985)). In the other pathological change, i.e., the neurofibrillary tangles, a double-helical filamentous substance called paired helical filament (abbreviated as "PHF" hereinafter in the specification) accumulate intracellularly, and tau protein, which is a kind of microtubule-associated protein specific for brain, has been revealed as its main component (Proc. Natl. Acad. Sci. USA, 85, 4506 (1988); Neuron, 1, 827 (1988)).

Furthermore, on the basis of genetic investigations, presenilins 1 and 2 were found as causative genes of familial Alzheimer disease (Nature, 375, 754 (1995); Science, 269, 973 (1995); Nature, 376, 775 (1995)), and it has been revealed that presence of mutants of presenilins 1 and 2 promotes the secretion of A β (Neuron, 17, 1005 (1996); Proc. Natl. Acad. Sci. USA, 94, 2025 (1997)). From these results, it is considered that, in Alzheimer disease, A β abnormally accumulates and agglomerates due to a certain reason, which engages with the formation of PHF to cause death of nerve cells. It is also expected that extracellular outflow of glutamic acid and activation of glutamate receptor responding to the outflow may possibly be important factors in an early process of the nerve cell death caused by ischemic cerebrovascular accidents (Sai-shin Igaku [Latest Medicine], 49, 1506 (1994)).

It has been reported that kainic acid treatment that stimulates the AMPA receptor, one of glutamate receptor, increases mRNA of the amyloid precursor protein (abbreviated as "APP" hereinafter in the specification) as a precursor of A β (Society for Neuroscience Abstracts, 17, 1445 (1991)), and also promotes metabolism of APP (The Journal of Neuroscience, 10, 2400 (1990)). Therefore, it has been strongly suggested that the accumulation of A β is involved in cellular death due to ischemic cerebrovascular disorders. Other diseases in which abnormal accumulation and agglomeration of A β are observed include, for example, Down syndrome, cerebral bleeding due to solitary cerebral amyloid angiopathy, Lewy body disease (Shin-kei Shinpo [Nerve Advance], 34, 343 (1990); Tanpaku-shitu Kaku-san Koso [Protein, Nucleic Acid, Enzyme], 41, 1476 (1996)) and the like. Furthermore, as diseases showing neurofibrillary tangles due to the PHF accumulation, examples include progressive supranuclear palsy, subacute sclerosing panencephalitic parkinsonism, postencephalitic parkinsonism, pugilistic encephalitis, Guam

parkinsonism-dementia complex, Lewy body disease and the like (Tanpakushitu Kakusan Koso [Protein, Nucleic Acid, Enzyme], 36, 2 (1991); Igaku no Ayumi [Progress of Medicine], 158, 511 (1991); Tanpakushitu Kakusan Koso [Protein, Nucleic Acid, Enzyme], 41, 1476 (1996)).

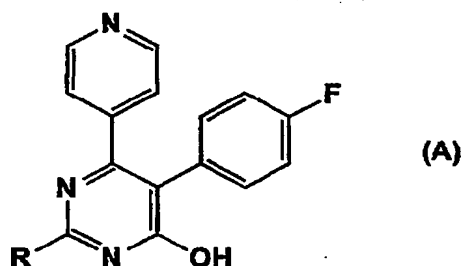
The tau protein is generally composed of a group of related proteins that forms several bands at molecular weights of 48-65 kDa in SDS-polyacrylamide gel electrophoresis, and it promotes the formation of microtubules. It has been verified that tau protein incorporated in the PHF in the brain suffering from Alzheimer disease is abnormally phosphorylated compared with usual tau protein (J. Biochem., 99, 1807 (1986); Proc. Natl. Acad. Sci. USA, 83, 4913 (1986)). An enzyme catalyzing the abnormal phosphorylation has been isolated. The protein was named as tau protein kinase 1 (abbreviated as "TPK1" hereinafter in the specification), and its physicochemical properties have been elucidated (Seikagaku [Biochemistry], 64, 308 (1992); J. Biol. Chem., 267, 10897 (1992)). Moreover, cDNA of rat TPK1 was cloned from a rat cerebral cortex cDNA library based on a partial amino acid sequence of TPK1, and its nucleotide sequence was determined and an amino acid sequence was deduced (Japanese Patent Un-examined Publication [Kokai] No. 6-239893/1994). As a result, it has been revealed that the primary structure of the rat TPK1 corresponds to that of the enzyme known as rat GSK-3 β (glycogen synthase kinase 3 β , FEBS Lett., 325, 167 (1993)).

It has been reported that A β , the main component of senile plaques, is neurotoxic (Science, 250, 279 (1990)). However, various theories have been proposed as for the reason why A β causes the cell death, and any authentic theory has not yet been established. Takashima et al. observed that the cell death was caused by A β treatment of fetal rat hippocampus primary culture system, and then found that the TPK1 activity was increased by A β treatment and the cell death by A β was inhibited by antisense of TPK1 (Proc. Natl. Acad. Sci. USA, 90, 7789 (1993); Japanese Patent Un-examined Publication [Kokai] No. 6-329551/1994).

In view of the foregoing, compounds which inhibit the TPK1 activity may possibly suppress the neurotoxicity of A β and the formation of PHF and inhibit the nerve cell death in the Alzheimer disease, thereby cease or defer the progress of the disease. The compounds may also be possibly used as a medicament for therapeutic

treatment of ischemic cerebrovascular disorder, Down syndrome, cerebral amyloid angiopathy, cerebral bleeding due to Lewy body disease and the like by suppressing the cytotoxicity of $A\beta$. Furthermore, the compounds may possibly be used as a medicament for therapeutic treatment of neurodegenerative diseases such as progressive supranuclear palsy, subacute sclerosing panencephalitic parkinsonism, postencephalitic parkinsonism, pugilistic encephalitis, Guam parkinsonism-dementia complex, Lewy body disease, Pick's disease, corticobasal degeneration, frontotemporal dementia, vascular dementia, acute stroke and traumatic injuries, brain and spinal cord trauma, peripheral neuropathies, retinopathies and glaucoma; non-insulin dependent diabetes (such as diabetes type II), and obesity, manic depressive illness, schizophrenia, alopecia, cancers such as breast cancer, non-small cell lung carcinoma, thyroid cancer, T or B-cell leukemia and several virus-induced tumors.

As structurally similar compounds to the compounds of the present invention represented by formula (I) described later, compounds represented by the following formula (A) are known:



wherein R represents 2,6-dichlorobenzyl group, 2-(2-chlorophenyl)ethylamino group, 3-phenylpropylamino group, or 1-methyl-3-phenylpropylamino group (W098/24782). The compounds represented by formula (A) are characterized to have 4-fluorophenyl group at the 5-position of the pyrimidine ring and a hydroxy group at the 4-position, and not falling within the scope of the present invention. Moreover, main pharmacological activity of the compounds represented by formula (A) is anti-inflammatory effect, whereas the compounds of the present invention represented by formula (I) are useful as a TPK1 inhibitor or a medicament for

therapeutic treatment of neurodegenerative diseases, and therefore, their pharmacological activities are totally different to each other.

Patent Document 1: WO 00/18758

Patent Document 2: WO 01/70728

Patent Document 3: WO 01/70729

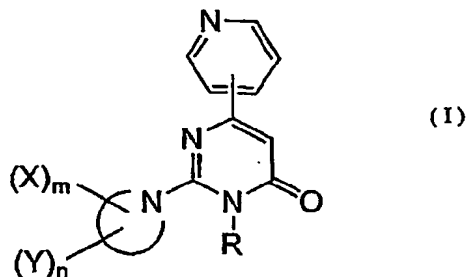
Object to be Achieved by the Invention

An object of the present invention is to provide compounds useful as an active ingredient of a medicament for preventive and/or therapeutic treatment of diseases such as Alzheimer disease. More specifically, the object is to provide novel compounds useful as an active ingredient of a medicament that enables radical prevention and/or treatment of the neurodegenerative diseases such as Alzheimer disease by inhibiting the TPK1 activity to suppress the neurotoxicity of A β and the formation of the PHF and by inhibiting the death of nerve cells.

Means to Achieve the Object

In order to achieve the foregoing object, the inventors of the present invention conducted screenings of various compounds having inhibitory activity against the phosphorylation of TPK1. As a result, they found that compounds represented by the following formula (I) had the desired activity and were useful as an active ingredient of a medicament for preventive and/or therapeutic treatment of the aforementioned diseases. The present invention was achieved on the basis of these findings.

The present invention thus provides 3-substituted-4-pyrimidone derivatives represented by formula (I) or salts thereof, or solvates thereof or hydrates thereof:



wherein R represents a C₁-C₁₂ alkyl group which may be substituted;
the ring of:



represents piperazine ring or piperidine ring;

each X independently represents a C₁-C₈ alkyl group which may be substituted, an optionally partially hydrogenated C₆-C₁₀ aryl ring which may be substituted, an indan ring which may be substituted, an optionally substituted heterocyclic ring having 1 to 4 hetero atoms selected from the group consisting of oxygen atom, sulfur atom, and nitrogen atom, and having 5 to 10 ring-constituting atoms in total, a phenylamino group which may be substituted or X¹-CO- wherein X¹ represents a C₆-C₁₀ aryl ring which may be substituted or a C₁-C₈ alkyl group which may be substituted;

m represents an integer of 1 to 3;

each Y independently represents a halogen atom, a hydroxy group, a cyano group, a C₁-C₈ alkyl group which may be substituted, Y¹-CO- wherein Y¹ represents a C₆-C₁₀ aryl ring which may be substituted or a C₁-C₈ alkyl group which may be substituted or Y²-O-CO- wherein Y² represents a C₁-C₈ alkyl group which may be substituted;

n represents an integer of 0 to 8;

when X and Y or two Y groups are attached on the same carbon atom, they may combine to each other to form a C₂-C₈ alkylene group;

and when m is 1, n is 0, and X is X¹-CO-,

- (1) X does not bind to 3-position of unsubstituted 1-piperazinyl group or does not bind to 3-position of a 4-alkyl-1-piperazinyl group; or
- (2) X does not bind to 3-position or 4-position of non-substituted 1-piperidinyl group.

According to another aspect of the present invention, there is provided a medicament comprising as an active ingredient a substance selected from the group consisting of the 3-substituted-4-pyrimidone derivatives represented by formula (I) and the physiologically acceptable salts thereof, and the solvates thereof and the hydrates thereof. As preferred embodiments of the medicament, there are provided the aforementioned medicament which is used for preventive and/or therapeutic treatment of diseases caused by tau protein kinase 1 hyperactivity, and the aforementioned medicament which is used for preventive and/or therapeutic treatment of neurodegenerative diseases.

As further preferred embodiments of the present invention, there are provided the aforementioned medicament wherein the diseases are selected from the group consisting of Alzheimer disease, ischemic cerebrovascular accidents, Down syndrome, cerebral bleeding due to cerebral amyloid angiopathy, progressive supranuclear palsy, subacute sclerosing panencephalitic parkinsonism, postencephalitic parkinsonism, pugilistic encephalitis, Guam parkinsonism-dementia complex, Lewy body disease, Pick's disease, corticobasal degeneration and frontotemporal dementia, vascular dementia, acute stroke and traumatic injuries, brain and spinal cord trauma, peripheral neuropathies, retinopathies and glaucoma, non-insulin dependent diabetes (such as diabetes type II), and obesity, manic depressive illness, schizophrenia, alopecia, cancers such as breast cancer, non-small cell lung carcinoma, thyroid cancer, T or B-cell leukemia and several virus-induced tumors; and the aforementioned medicament in the form of pharmaceutical composition containing the above substance as an active ingredient together with one or more pharmaceutical additives.

The present invention further provides an inhibitor of tau protein kinase 1 comprising as an active ingredient a substance selected from the group consisting of the 3-substituted-4-pyrimidone derivatives of formula (I) and the salts thereof, and the solvates thereof and the hydrates thereof.

According to further aspects of the present invention, there are provided a method for preventive and/or therapeutic treatment of diseases caused by tau protein kinase 1 hyperactivity, which comprises the step of administering to a

patient a preventively and/or therapeutically effective amount of a substance selected from the group consisting of the 3-substituted-4-pyrimidone derivatives of formula (I) and the physiologically acceptable salts thereof, and the solvates thereof and the hydrates thereof; and a use of a substance selected from the group consisting of the 3-substituted-4-pyrimidone derivatives of formula (I) and the physiologically acceptable salts thereof, and the solvates thereof and the hydrates thereof for the manufacture of the aforementioned medicament.

Mode for Carrying Out the Invention

The alkyl group used herein may be either linear or branched.

The C₁-C₁₂ alkyl group represented by R may be, for example, methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, isobutyl group, sec-butyl group, tert-butyl group, n-pentyl group, isopentyl group, neopentyl group, 1,1-dimethylpropyl group, n-hexyl group, isohexyl group, or a linear or branched heptyl group, octyl group, nonyl group, decyl group, undecyl group or dodecyl group. Particularly preferred R is methyl group.

In the specification, when a functional group is defined as "which may be substituted" or "optionally substituted", the number of substituents as well as their types and substituting positions are not particularly limited, and when two or more substituents are present, they may be the same or different.

When the C₁-C₁₂ alkyl group represented by R has one or more substituents, the alkyl group may have one or more substituents selected from, for example, the groups consisting of a C₃-C₈ cycloalkyl group such as cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group, cycloheptyl group, cyclooctyl group; a C₁-C₅ alkoxy group such as methoxy group, ethoxy group, propoxy group, isopropoxy group, butoxy group, isobutoxy group, tert-butoxy group; C₁-C₃ alkylamino group or C₂-C₆ dialkylamino group; a C₆-C₁₀ aryl group such as phenyl group, 1-naphthyl group, and 2-naphthyl group.

The C₁-C₈ alkyl group represented by X may be, for example, methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, isobutyl group, sec-butyl group, tert-butyl group, n-pentyl group, isopentyl group, neopentyl group, 1,1-dimethylpropyl group, n-hexyl group, isohexyl group, or a linear or branched

heptyl group or octyl group.

The optionally partially hydrogenated C₆-C₁₀ aryl ring represented by X may be, for example a benzene ring, a naphthalene ring, an indan ring or a 1,2,3,4-tetrahydronaphthalene ring.

The heterocyclic ring having 1 to 4 hetero atoms selected from the group consisting of oxygen atom, sulfur atom, and nitrogen atom, and having 5 to 10 ring-constituting atoms in total represented by X may be, for example, furan ring, dihydrofuran ring, tetrahydrofuran ring, pyran ring, dihydropyran ring, tetrahydropyran ring, benzofuran ring, dihydrobenzofuran, isobenzofuran ring, benzodioxol ring, chromene ring, chroman ring, isochroman ring, thiophene ring, benzothiophene ring, pyrrole ring, pyrroline ring, pyrrolidine ring, imidazole ring, imidazoline ring, imidazolidine ring, pyrazole ring, pyrazoline ring, pyrazolidine ring, triazole ring, tetrazole ring, pyridine ring, pyridine oxide ring, piperidine ring, pyrazine ring, piperazine ring, pyrimidine ring, pyridazine ring, indole ring, indoline ring, isoindole ring, isoindoline ring, indazole ring, benzimidazole ring, benzotriazole ring, tetrahydroisoquinoline ring, benzothiazolinone ring, benzoxazolinone ring, purine ring, quinolizine ring, quinoline ring, phthalazine ring, naphthyridine ring, quinoxaline ring, quinazoline ring, cinnoline ring, pteridine ring, oxazole ring, oxazolidine ring, isoxazole ring, isoxazolidine ring, oxadiazole ring, thiazole ring, benzothiazole ring, thiazylidine ring, isothiazole ring, isothiazolidine ring, benzodioxole ring, dioxane ring, benzodioxane ring, dithian ring, morpholine ring, thiomorpholine ring, or phthalimide ring.

The C₆-C₁₀ aryl ring represented by X¹ or Y¹ may be, for example, a benzene ring or a naphthalene ring.

When the ring represented by X or X¹ has one or more substituents, the ring may have one or more substituents selected from the group consisting of a C₁-C₅ alkyl group such as methyl group, ethyl group, propyl group, isopropyl group, butyl group, isobutyl group, sec-butyl group, tert-butyl group, pentyl group, isopentyl group, neopentyl group, 1,1-dimethylpropyl group; C₃-C₆ cycloalkyl group such as cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group; a C₃-C₆ cycloalkyloxy group such as cyclopropyloxy group, cyclobutyloxy group, cyclopentyloxy group, cyclohexyloxy group; a C₁-C₆ alkoxy group such as methoxy

group, ethoxy group, propoxy group, isopropoxy group, butoxy group, isobutoxy group, tert-butoxy group, pentyloxy group, and isopentyloxy group; a C₄-C₇ cycloalkylalkoxyl group such as cyclopropylmethoxy group, cyclopentylmethoxy group; a C₁-C₅ alkylthio group such as methylthio group, ethylthio group, propylthio group, butylthio group, and pentylthio group; a C₁-C₅ alkylsulfonyl group such as methanesulfonyl group, ethanesulfonyl group, propanesulfonyl group, butanesulfonyl group, and pentanesulfonyl group; a halogen atom such as fluorine atom, chlorine atom, bromine atom, and iodine atom; a C₁-C₅ halogenated alkyl group such as trifluoromethyl group; hydroxyl group; cyano group; nitro group; formyl group; a C₂-C₆ alkylcarbonyl group such as acetyl group, propionyl group, butyryl group, and valeryl group; a benzene ring which may be substituted, a naphthalene ring which may be substituted, an optionally substituted heterocyclic ring having 1 to 4 hetero atoms selected from the group consisting of oxygen atom, sulfur atom and nitrogen atom, and having 5 to 10 ring-constituting atoms in total; a phenoxy group which may be substituted; a phenylamino group which may be substituted; an amino group; a C₁-C₅ monoalkylamino group such as methylamino group, ethylamino group, propylamino group, isopropylamino group, butylamino group, isobutylamino group, tert-butylamino group, pentylamino group, and isopentylamino group; a C₂-C₁₀ dialkylamino group such as dimethylamino group, ethylmethylamino group, diethylamino group, methylpropylamino group, and diisopropylamino group; a C₁-C₆ monoalkylaminomethyl group such as methylaminomethyl group, ethylaminomethyl group, propylaminomethyl group, isopropylaminomethyl group, butylaminomethyl group, isobutylaminomethyl group, tert-butylaminomethyl group, pentylaminomethyl group, isopentylaminomethyl; a C₂-C₁₀ dialkylaminomethyl group such as dimethylaminomethyl group, diethylaminomethyl group, ethylmethylaminomethyl group, methylpropylaminomethyl group; pyrrolidinylmethyl group; piperidinylmethyl group; morpholinomethyl group; piperazinylmethyl group; pyrrolylmethyl group; imidazolylmethyl group; pyrazolylmethyl group; and triazolylmethyl group.

When the C₆-C₁₀ aryl ring represented by Y¹ has one or more substituents, the ring may be substituted by one or more substituents selected from the groups consisting of halogen atoms, a C₁-C₅ alkyl group, a C₃-C₆ cycloalkyl group, a C₈-C₆

cycloalkyloxy group, a C₁-C₅ alkoxy group, a C₄-C₇ cycloalkylalkoxy, a C₁-C₅ alkylthio group, a C₁-C₅ alkylsulfonyl group, a C₁-C₅ halogenated alkyl, and a benzene ring.

When the ring represented by X, X¹ or Y¹ has one or more substituents, the substituent may further have one or more substituents selected from the group consisting of a C₁-C₅ alkyl group such as methyl group, ethyl group, propyl group, isopropyl group, butyl group, isobutyl group, sec-butyl group, tert-butyl group, pentyl group, isopentyl group, neopentyl group, 1,1-dimethylpropyl group; C₃-C₆ cycloalkyl group such as cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group; a C₃-C₆ cycloalkyloxy group such as cyclopropyloxy group, cyclobutyloxy group, cyclopentyloxy group, cyclohexyloxy group; hydroxy group; a C₁-C₅ alkoxy group such as methoxy group, ethoxy group, propoxy group, isopropoxy group, butoxy group, isobutoxy group, tert-butoxy group, pentyloxy group, and isopentyloxy group; a C₄-C₇ cycloalkylalkoxy group such as cyclopropylmethoxy group, cyclopentylmethoxy group; a C₁-C₅ alkylthio group such as methylthio group, ethylthio group, propylthio group, butylthio group, and pentylthio group; a C₁-C₅ alkylsulfonyl group such as methanesulfonyl group, ethanesulfonyl group, propanesulfonyl group, butanesulfonyl group, and pentanesulfonyl group; a halogen atom such as fluorine atom, chlorine atom, bromine atom, and iodine atom; a C₁-C₅ halogenated alkyl group such as trifluoromethyl group; a C₁-C₅ halogenated alkoxy group such as trifluoromethoxy group, 2,2,2-trifluoroethoxy group; hydroxyl group; cyano group; nitro group; formyl group; a C₂-C₆ alkylcarbonyl group such as acetyl group, propionyl group, butyryl group, and valeryl group; amino group; a C₁-C₅ monoalkylamino group such as methylamino group, ethylamino group, propylamino group, isopropylamino group, butylamino group, isobutylamino group, tert-butylamino group, pentylamino group, and isopentylamino group; a C₂-C₁₀ dialkylamino group such as dimethylamino group, ethylmethylamino group, diethylamino group, methylpropylamino group, and diisopropylamino group; a C₂-C₁₀ monoalkylaminomethyl group such as methylaminomethyl group, ethylaminomethyl group, propylaminomethyl group, isopropylaminomethyl group, butylaminomethyl group, isobutylaminomethyl group, tert-butylaminomethyl group, pentylaminomethyl group, isopentylaminomethyl; a C₃-C₁₁

dialkylaminomethyl group such as dimethylaminomethyl group, diethylaminomethyl group, ethylmethylaminomethyl group, methylpropylaminomethyl group and the like.

R may preferably be a C₁-C₈ alkyl group, more preferably a methyl group or an ethyl group. The substituent of the alkyl group may preferably be a C₃-C₈ alkyl group.

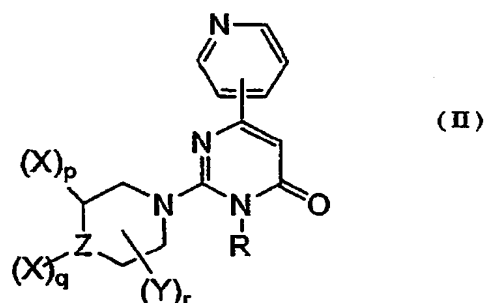
X may preferably be a benzene ring which may be substituted, a benzyl group which may be substituted, a naphthyl group which may be substituted, a benzofuran ring which may be substituted, a dihydrobenzofuran ring which may be substituted, a benzoxazole ring which may be substituted, a benzisoxazole ring which may be substituted, a benzothiazole ring which may be substituted, a benzisothiazole ring which may be substituted, and a benzopyrazole ring which may be substituted; more preferably a benzene ring which may be substituted, a benzyl group which may be substituted. Substituent of X may preferably be selected from the group consisting of a halogen atom, a C₁-C₄ alkyl group, a C₁-C₄ alkoxy group, a hydroxy group, a nitro group, a cyano group, a perhalogenated C₁-C₄ alkyl group, a carboxyl group, a C₁-C₄ alkoxycarbonyl group, a C₁-C₄ alkylthio group, a C₁-C₄ alkoxysulfonyl group, and amino group which may be substituted by a C₁-C₄ alkyl group.

The compounds represented by the aforementioned formula (I) may form a salt. Examples of the salt include, when an acidic group exists, salts of alkali metals and alkaline earth metals such as lithium, sodium, potassium, magnesium, and calcium; salts of ammonia and amines such as methylamine, dimethylamine, trimethylamine, dicyclohexylamine, tris(hydroxymethyl)aminomethane, N,N-bis(hydroxyethyl)piperazine, 2-amino-2-methyl-1-propanol, ethanolamine, N-methylglucamine, and L-glucamine; or salts with basic amino acids such as lysine, δ -hydroxylysine, and arginine. When a basic group exists, examples include salts with mineral acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid; salts with organic acids such as methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, acetic acid, propionic acid, tartaric acid, fumaric acid, maleic acid, malic acid, oxalic acid, succinic acid, citric acid, benzoic acid, mandelic acid, cinnamic acid, lactic acid,

glycolic acid, glucuronic acid, ascorbic acid, nicotinic acid, and salicylic acid; or salts with acidic amino acids such as aspartic acid, and glutamic acid.

In addition to the 3-substituted-4-pyrimidone derivatives represented by the aforementioned formula (I) and salts thereof, their solvates and hydrates also fall within the scope of the present invention. The 3-substituted-4-pyrimidone derivatives represented by the aforementioned formula (I) may have one or more asymmetric carbon atoms. As for the stereochemistry of such asymmetric carbon atoms, they may independently be in either (R) and (S) configuration, and the pyrimidone derivative may exist as stereoisomers such as optical isomers, or diastereoisomers. Any stereoisomers in a pure form, any mixtures of stereoisomers, racemates and the like fall within the scope of the present invention.

Preferred compounds of the present invention are represented by formula (II):



wherein R, X, Y are the same as those defined above; p is 0 or 1; q is 0 or 1; r is an integer of 0 to 6; p+q is 1 or 2;

and Z represents N or CZ¹ wherein Z¹ represents hydrogen atom or Y.

Examples of more preferred classes of compounds represented by formula (II) include:

- (1) those wherein R represents a C₁-C₃ alkyl group which may be substituted by a C₃-C₈ cycloalkyl group;
- (2) the compounds of the above (1) wherein R is methyl group or ethyl group; Y is in 3-, 4- or 5-position of the piperazine ring or the piperidine ring; p+q is 1; and r is an integer of 0 to 3;
- (3) the compounds of the above (2) wherein X is a C₁-C₈ alkyl group which may be substituted or a C₆-C₁₀ aryl ring which may be substituted; Y is a C₁-C₆ alkyl group which may be substituted; p is 1; q is 0; r is an integer of 0 to 3; and Z is N or CH;

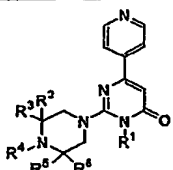
















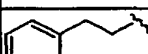



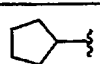
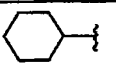
- (4) the compounds of the above (3) wherein X is a benzene ring which may be substituted, a benzyl group which may be substituted; Y is a methyl group which may be substituted; Z is N and r is 0 or 1;
- (5) the compounds of the above (2) wherein X is a benzene ring which may be substituted, a benzyl group which may be substituted, a benzoyl group which may be substituted, or a benzisothiazol ring which may be substituted; Y is a methyl group which may be substituted; Z is N and p is 0;
- (6) the compounds of the above (2) wherein X is a C₁-C₈ alkyl group substituted by a benzene ring which may be substituted or a benzene ring which may be substituted; Y is a hydroxy group, a cyano group, or Y¹-CO- wherein Y¹ is a C₁-C₈ alkyl group; Z is CH or C-Y and r is 0 or 1; and
- (7) the compounds of the above (6) wherein X is a benzyl group which may be substituted or a benzene ring which may be substituted; Y is a hydroxy group, a cyano group, or an acetyl group; Z is CH or C-Y and r is 0 or 1.

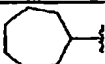





















Examples of particularly preferred classes of compounds represented by formula (II) include:


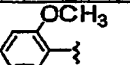
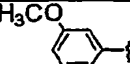
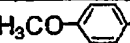
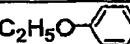
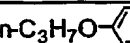
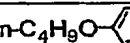
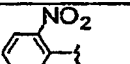

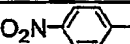
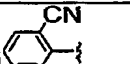
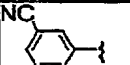
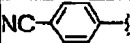
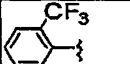
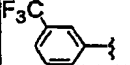
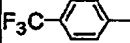
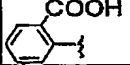
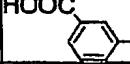

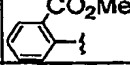
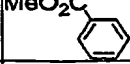
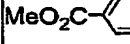
- (1) those wherein R is methyl group, Y is CH₃O-CO- group or CH₃CH₂O-CO- group, Z is N, p is 0, q is 1, r is 0 or 1 and Y is in 3-position of the piperazine ring;
- (2) those wherein R is methyl group, Y is methyl group, benzyl group or acetyl group, Z is N, p is 1, q is 0, r is 0 or 1 and Y is in 4-position of the piperazine ring;
- (3) those wherein R is methyl group, Y is methyl group, Z is N, p is 1, q is 0, r is 1 to 3 and Y is in 3-, 4-, or 5-position of the piperazine ring;
- (4) those wherein R is methyl group, Y is hydroxyl group or cyano group, Z is CH, p is 1, q is 0, r is 0 or 1 and X and Y are attached on the same carbon atom;
- (5) those wherein R is methyl group, Y is hydroxyl group, cyano group or acetyl group, Z is C-Y, p is 0, q is 1 and r is 1.

Examples of preferred compounds of the present invention are shown in the tables below. However, the scope of the present invention is not limited to the following compounds.























Table-1

						
No.	R1	R2	R3	R4	R5	R6
A1	CH3-	H	H	CH3-	H	H
A2	CH3-	H	H	CH3CH2-	H	H
A3	CH3-	H	H		H	H
A4	CH3-	H	H		H	H
A5	CH3-	H	H		H	H
A6	CH3-	H	H		H	H
A7	CH3-	H	H		H	H
A8	CH3-	H	H		H	H
A9	CH3-	H	H		H	H
A10	CH3-	H	H		H	H
A11	CH3-	H	H		H	H
A12	CH3-	H	H		H	H
A13	CH3-	H	H		H	H
A14	CH3-	H	H		H	H
A15	CH3-	H	H		H	H
A16	CH3-	H	H		H	H
A17	CH3-	H	H	n-C8H17-	H	H
A18	CH3-	H	H		H	H
A19	CH3-	H	H		H	H
A20	CH3-	H	H		H	H
A21	CH3-	H	H		H	H
A22	CH3-	H	H		H	H
A23	CH3-	H	H		H	H
A24	CH3-	H	H		H	H
A25	CH3-	H	H		H	H

No.	R1	R2	R3	R4	R5	R6
A26	CH ₃ -	H	H		H	H
A27	CH ₃ -	H	H		H	H
A28	CH ₃ -	H	H		H	H
A29	CH ₃ -	H	H		H	H
A30	CH ₃ -	H	H		H	H
A31	CH ₃ -	H	H		H	H
A32	CH ₃ -	H	H		H	H
A33	CH ₃ -	H	H		H	H
A34	CH ₃ -	H	H		H	H
A35	CH ₃ -	H	H		H	H
A36	CH ₃ -	H	H		H	H
A37	CH ₃ -	H	H		H	H
A38	CH ₃ -	H	H		H	H
A39	CH ₃ -	H	H		H	H
A40	CH ₃ -	H	H		H	H
A41	CH ₃ -	H	H		H	H
A42	CH ₃ -	H	H		H	H
A43	CH ₃ -	H	H		H	H
A44	CH ₃ -	H	H		H	H
A45	CH ₃ -	H	H		H	H
A46	CH ₃ -	H	H		H	H
A47	CH ₃ -	H	H		H	H

No.	R1	R2	R3	R4	R5	R6
A48	CH ₃ -	H	H		H	H
A49	CH ₃ -	H	H		H	H
A50	CH ₃ -	H	H		H	H
A51	CH ₃ -	H	H		H	H
A52	CH ₃ -	H	H		H	H
A53	CH ₃ -	H	H		H	H
A54	CH ₃ -	H	H		H	H
A55	CH ₃ -	H	H		H	H
A56	CH ₃ -	H	H		H	H
A57	CH ₃ -	H	H		H	H
A58	CH ₃ -	H	H		H	H
A59	CH ₃ -	H	H		H	H
A60	CH ₃ -	H	H		H	H
A61	CH ₃ -	H	H		H	H
A62	CH ₃ -	H	H		H	H
A63	CH ₃ -	H	H		H	H
A64	CH ₃ -	H	H		H	H
A65	CH ₃ -	H	H		H	H
A66	CH ₃ -	H	H		H	H
A67	CH ₃ -	H	H		H	H
A68	CH ₃ -	H	H		H	H
A69	CH ₃ -	H	H		H	H

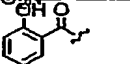
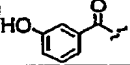
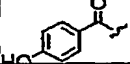
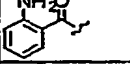
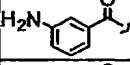
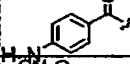
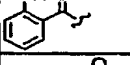
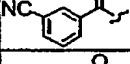
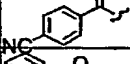
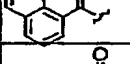
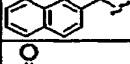
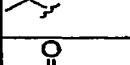
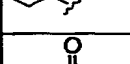
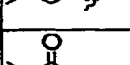
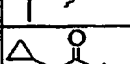
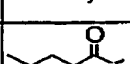
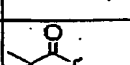
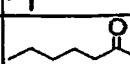
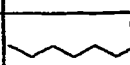
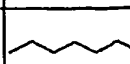
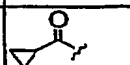

No.	R1	R2	R3	R4	R5	R6
A70	CH3-	H	H		H	H
A71	CH3-	H	H		H	H
A72	CH3-	H	H		H	H
A73	CH3-	H	H		H	H
A74	CH3-	H	H		H	H
A75	CH3-	H	H		H	H
A76	CH3-	H	H		H	H
A77	CH3-	H	H		H	H
A78	CH3-	H	H		H	H
A79	CH3-	H	H		H	H
A80	CH3-	H	H		H	H
A81	CH3-	H	H		H	H
A82	CH3-	H	H		H	H
A83	CH3-	H	H		H	H
A84	CH3-	H	H		H	H
A85	CH3-	H	H		H	H
A86	CH3-	H	H		H	H
A87	CH3-	H	H		H	H
A88	CH3-	H	H		H	H
A89	CH3-	H	H		H	H
A90	CH3-	H	H		H	H
A91	CH3-	H	H		H	H




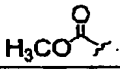
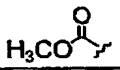
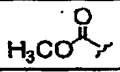
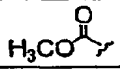

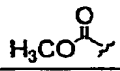

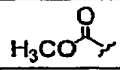

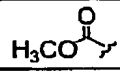

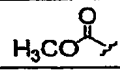

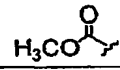

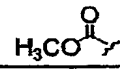

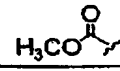
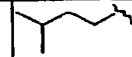
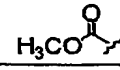

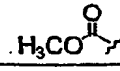

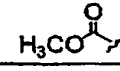

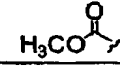
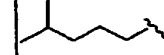
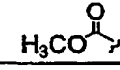
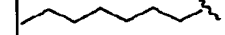
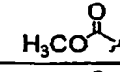
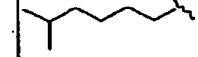
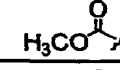
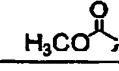
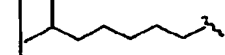
No.	R1	R2	R3	R4	R5	R6
A92	CH3-	H	H		H	H
A93	CH3-	H	H		H	H
A94	CH3-	H	H		H	H
A95	CH3-	H	H		H	H
A96	CH3-	H	H		H	H
A97	CH3-	H	H		H	H
A98	CH3-	H	H		H	H
A99	CH3-	H	H		H	H
A100	CH3-	H	H		H	H
A101	CH3-	H	H		H	H
A102	CH3-	H	H		H	H
A103	CH3-	H	H		H	H
A104	CH3-	H	H		H	H
A105	CH3-	H	H		H	H
A106	CH3-	H	H		H	H
A107	CH3-	H	H		H	H
A108	CH3-	H	H		H	H
A109	CH3-	H	H		H	H
A110	CH3-	H	H		H	H
A111	CH3-	H	H		H	H
A112	CH3-	H	H		H	H
A113	CH3-	H	H		H	H

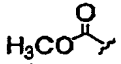
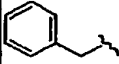
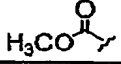
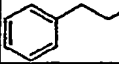
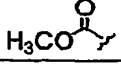
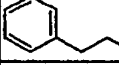
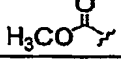

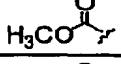

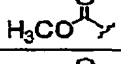

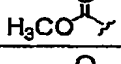

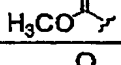

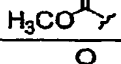

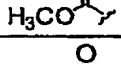

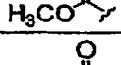

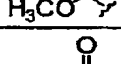

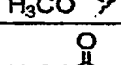

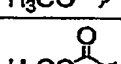

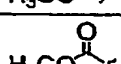

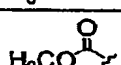

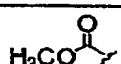

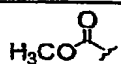

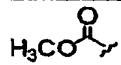

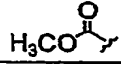

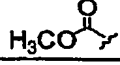



No.	R1	R2	R3	R4	R5	R6
A114	CH3-	H	H		H	H
A115	CH3-	H	H		H	H
A116	CH3-	H	H		H	H
A117	CH3-	H	H		H	H
A118	CH3-	H	H		H	H
A119	CH3-	H	H		H	H
A120	CH3-	H	H		H	H
A121	CH3-	H	H		H	H
A122	CH3-	H	H		H	H
A123	CH3-	H	H		H	H
A124	CH3-	H	H		H	H
A125	CH3-	H	H		H	H
A126	CH3-	H	H		H	H
A127	CH3-	H	H		H	H
A128	CH3-	H	H		H	H
A129	CH3-	H	H		H	H
A130	CH3-	H	H		H	H
A131	CH3-	H	H		H	H
A132	CH3-	H	H		H	H
A133	CH3-	H	H		H	H
A134	CH3-	H	H		H	H
A135	CH3-	H	H		H	H

No.	R1	R2	R3	R4	R5	R6
A136	CH3-	H	H		H	H
A137	CH3-	H	H		H	H
A138	CH3-	H	H		H	H
A139	CH3-	H	H		H	H
A140	CH3-	H	H		H	H
A141	CH3-	H	H		H	H
A142	CH3-	H	H		H	H
A143	CH3-	H	H		H	H
A144	CH3-	H	H		H	H
A145	CH3-	H	H		H	H
A146	CH3-	H	H		H	H
A147	CH3-	H	H		H	H
A148	CH3-	H	H		H	H
A149	CH3-	H	H		H	H
A150	CH3-	H	H		H	H
A151	CH3-	H	H		H	H
A152	CH3-	H	H		H	H
A153	CH3-	H	H		H	H
A154	CH3-	H	H		H	H
A155	CH3-	H	H		H	H
A156	CH3-	H	H		H	H
A157	CH3-	H	H		H	H

No.	R1	R2	R3	R4	R5	R6
A158	CH3-	H	H		H	H
A159	CH3-	H	H		H	H
A160	CH3-	H	H		H	H
A161	CH3-	H	H		H	H
A162	CH3-	H	H		H	H
A163	CH3-	H	H		H	H
A164	CH3-	H	H		H	H
A165	CH3-	H	H		H	H
A166	CH3-	H	H		H	H
A167	CH3-	H	H		H	H
A168	CH3-	H	H		H	H
A169	CH3-	H	H		H	H
A170	CH3-	H	H		H	H
A171	CH3-	H	H		H	H
A172	CH3-	H	H		H	H
A173	CH3-	H	H		H	H
A174	CH3-	H	H		H	H
A175	CH3-	H	H		H	H
A176	CH3-	H	H		H	H
A177	CH3-	H	H		H	H
A178	CH3-	H	H		H	H
A179	CH3-	H	H		H	H

No.	R1	R2	R3	R4	R5	R6
A180	CH3-	H	H		H	H
A181	CH3-	H	H		H	H
A182	CH3-	H	H		H	H
A183	CH3-	H	H		H	H
A184	CH3-	H	H		H	H
A185	CH3-	H	H		H	H
A186	CH3-	H	H		H	H
A187	CH3-	H	H		H	H
A188	CH3-	H	H		H	H
A189	CH3-	H	H		H	H
A190	CH3-	H	H		H	H
A191	CH3-	H	H		H	H
A192	CH3-	H	H		H	H
A193	CH3-	H	H		H	H
A194	CH3-	H	H		H	H
A195	CH3-	H	H		H	H
A196	CH3-	H	H		H	H
A197	CH3-	H	H		H	H
A198	CH3-	H	H		H	H
A199	CH3-	H	H		H	H
A200	CH3-	H	H		H	H
A201	CH3-	H	H		H	H

No.	R1	R2	R3	R4	R5	R6
A202	CH3-	H	H		H	H
A203	CH3-	H	H		H	H
A204	CH3-	H	H		H	H
A205	CH3-		H	H	H	H
A206	CH3-		H	CH3-	H	H
A207	CH3-		H	CH3CH2-	H	H
A208	CH3-		H		H	H
A209	CH3-		H		H	H
A210	CH3-		H		H	H
A211	CH3-		H		H	H
A212	CH3-		H		H	H
A213	CH3-		H		H	H
A214	CH3-		H		H	H
A215	CH3-		H		H	H
A216	CH3-		H		H	H
A217	CH3-		H		H	H
A218	CH3-		H		H	H
A219	CH3-		H		H	H
A220	CH3-		H		H	H
A221	CH3-		H		H	H
A222	CH3-		H	n-C8H17-	H	H
A223	CH3-		H		H	H

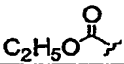








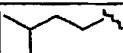



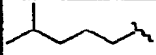


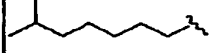
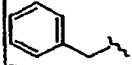
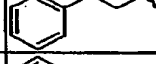
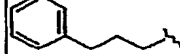
No.	R1	R2	R3	R4	R5	R6
A224	CH ₃ -		H		H	H
A225	CH ₃ -		H		H	H
A226	CH ₃ -		H		H	H
A227	CH ₃ -		H		H	H
A228	CH ₃ -		H		H	H
A229	CH ₃ -		H		H	H
A230	CH ₃ -		H		H	H
A231	CH ₃ -		H		H	H
A232	CH ₃ -		H		H	H
A233	CH ₃ -		H		H	H
A234	CH ₃ -		H		H	H
A235	CH ₃ -		H		H	H
A236	CH ₃ -		H		H	H
A237	CH ₃ -		H		H	H
A238	CH ₃ -		H		H	H
A239	CH ₃ -		H		H	H
A240	CH ₃ -		H		H	H
A241	CH ₃ -		H		H	H
A242	CH ₃ -		H		H	H
A243	CH ₃ -		H		H	H
A244	CH ₃ -		H		H	H
A245	CH ₃ -		H		H	H





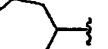
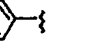
















No.	R1	R2	R3	R4	R5	R6
A246	CH ₃ -		H		H	H
A247	CH ₃ -		H		H	H
A248	CH ₃ -		H		H	H
A249	CH ₃ -		H		H	H
A250	CH ₃ -		H		H	H
A251	CH ₃ -		H		H	H
A252	CH ₃ -		H		H	H
A253	CH ₃ -		H		H	H
A254	CH ₃ -		H		H	H
A255	CH ₃ -		H		H	H
A256	CH ₃ -		H		H	H
A257	CH ₃ -		H		H	H
A258	CH ₃ -		H		H	H
A259	CH ₃ -		H		H	H
A260	CH ₃ -		H		H	H
A261	CH ₃ -		H		H	H
A262	CH ₃ -		H		H	H
A263	CH ₃ -		H		H	H
A264	CH ₃ -		H		H	H
A265	CH ₃ -		H		H	H
A266	CH ₃ -		H		H	H
A267	CH ₃ -		H		H	H

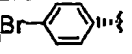




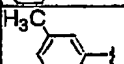
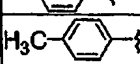
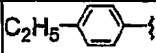
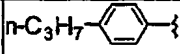
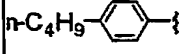

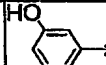
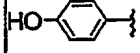
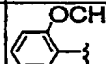
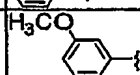
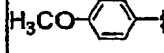
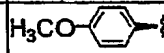
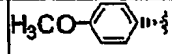
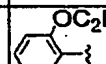
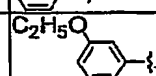
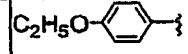
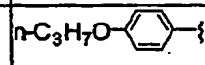
No.	R1	R2	R3	R4	R5	R6
A268	CH3-		H		H	H
A269	CH3-		H		H	H
A270	CH3-		H	H	H	H
A271	CH3-		H	CH3-	H	H
A272	CH3-		H	CH3CH2-	H	H
A273	CH3-		H		H	H
A274	CH3-		H		H	H
A275	CH3-		H		H	H
A276	CH3-		H		H	H
A277	CH3-		H		H	H
A278	CH3-		H		H	H
A279	CH3-		H		H	H
A280	CH3-		H		H	H
A281	CH3-		H		H	H
A282	CH3-		H		H	H
A283	CH3-		H		H	H
A284	CH3-		H		H	H
A285	CH3-		H		H	H
A286	CH3-		H		H	H
A287	CH3-		H	n-C8H17-	H	H
A288	CH3-		H		H	H
A289	CH3-		H		H	H

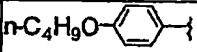

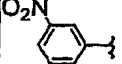
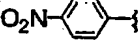


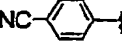

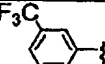
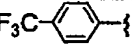
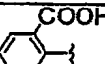
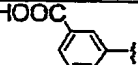
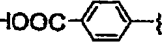
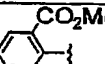
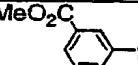
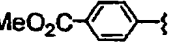
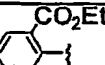
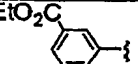
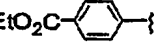

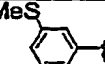
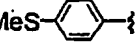
No.	R1	R2	R3	R4	R5	R6
A290	CH ₃ -		H		H	H
A291	CH ₃ -		H		H	H
A292	CH ₃ -		H		H	H
A293	CH ₃ -		H		H	H
A294	CH ₃ -		H		H	H
A295	CH ₃ -		H		H	H
A296	CH ₃ -		H		H	H
A297	CH ₃ -		H		H	H
A298	CH ₃ -		H		H	H
A299	CH ₃ -		H		H	H
A300	CH ₃ -		H		H	H
A301	CH ₃ -		H		H	H
A302	CH ₃ -		H		H	H
A303	CH ₃ -		H		H	H
A304	CH ₃ -		H		H	H
A305	CH ₃ -		H		H	H
A306	CH ₃ -		H		H	H
A307	CH ₃ -		H		H	H
A308	CH ₃ -		H		H	H
A309	CH ₃ -		H		H	H
A310	CH ₃ -		H		H	H
A311	CH ₃ -		H		H	H

No.	R1	R2	R3	R4	R5	R6
A312	CH ₃ -		H		H	H
A313	CH ₃ -		H		H	H
A314	CH ₃ -		H		H	H
A315	CH ₃ -		H		H	H
A316	CH ₃ -		H		H	H
A317	CH ₃ -		H		H	H
A318	CH ₃ -		H		H	H
A319	CH ₃ -		H		H	H
A320	CH ₃ -		H		H	H
A321	CH ₃ -		H		H	H
A322	CH ₃ -		H		H	H
A323	CH ₃ -		H		H	H
A324	CH ₃ -		H		H	H
A325	CH ₃ -		H		H	H
A326	CH ₃ -		H		H	H
A327	CH ₃ -		H		H	H
A328	CH ₃ -		H		H	H
A329	CH ₃ -		H		H	H
A330	CH ₃ -		H		H	H
A331	CH ₃ -		H		H	H
A332	CH ₃ -		H		H	H
A333	CH ₃ -		H		H	H

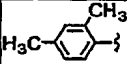
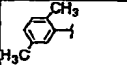
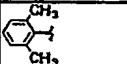
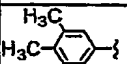
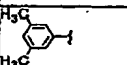
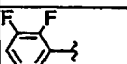
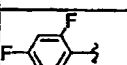
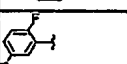
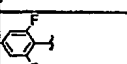
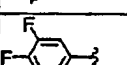
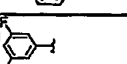
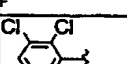
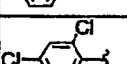
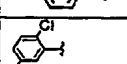
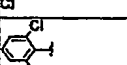
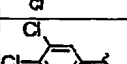
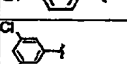
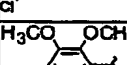
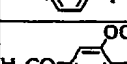
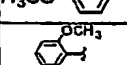
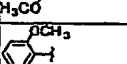
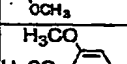
No.	R1	R2	R3	R4	R5	R6
A334	CH3-		H		H	H
A335	CH3-	CH3-	H	H	H	H
A336	CH3-	CH3CH2-	H	H	H	H
A337	CH3-		H	H	H	H
A338	CH3-		H	H	H	H
A339	CH3-		H	H	H	H
A340	CH3-		H	H	H	H
A341	CH3-		H	H	H	H
A342	CH3-		H	H	H	H
A343	CH3-		H	H	H	H
A344	CH3-		H	H	H	H
A345	CH3-		H	H	H	H
A346	CH3-		H	H	H	H
A347	CH3-		H	H	H	H
A348	CH3-		H	H	H	H
A349	CH3-		H	H	H	H
A350	CH3-		H	H	H	H
A351	CH3-	n-C8H17-	H	H	H	H
A352	CH3-		H	H	H	H
A353	CH3-		H	H	H	H
A354	CH3-		H	H	H	H
A355	CH3-		H	H	H	H

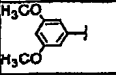
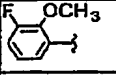
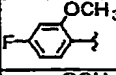
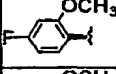
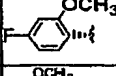
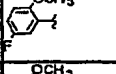
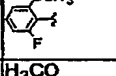
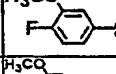
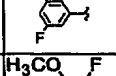
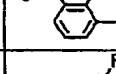
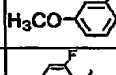
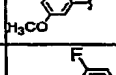
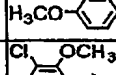
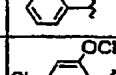
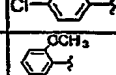
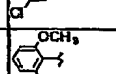
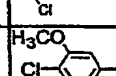
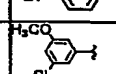
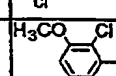
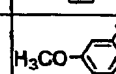
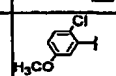

No.	R1	R2	R3	R4	R5	R6
A356	CH3-		H	H	H	H
A357	CH3-		H	H	H	H
A358	CH3-		H	H	H	H
A359	CH3-		H	H	H	H
A360	CH3-		H	H	H	H
A361	CH3-		H	H	H	H
A362	CH3-		H	H	H	H
A363	CH3-		H	H	H	H
A364	CH3-		H	H	H	H
A365	CH3-		H	H	H	H
A366	CH3-		H	H	H	H
A367	CH3-		H	H	H	H
A368	CH3-		H	H	H	H
A369	CH3-		H	H	H	H
A370	CH3-		H	H	H	H
A371	CH3-		H	H	H	H
A372	CH3-		H	H	H	H
A373	CH3-		H	H	H	H
A374	CH3-		H	H	H	H
A375	CH3-		H	H	H	H
A376	CH3-		H	H	H	H
A377	CH3-		H	H	H	H

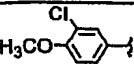
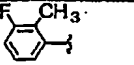
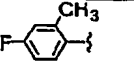
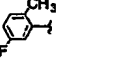
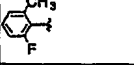
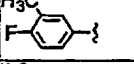
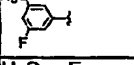
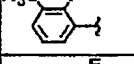
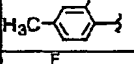
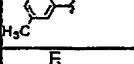
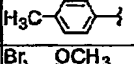
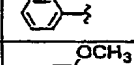
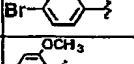
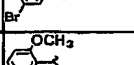
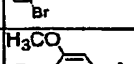
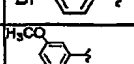
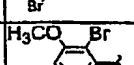
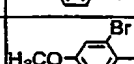
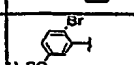
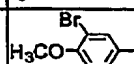
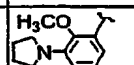

No.	R1	R2	R3	R4	R5	R6
A378	CH3-		H	H	H	H
A379	CH3-		H	H	H	H
A380	CH3-		H	H	H	H
A381	CH3-		H	H	H	H
A382	CH3-		H	H	H	H
A383	CH3-		H	H	H	H
A384	CH3-		H	H	H	H
A385	CH3-		H	H	H	H
A386	CH3-		H	H	H	H
A387	CH3-		H	H	H	H
A388	CH3-		H	H	H	H
A389	CH3-		H	H	H	H
A390	CH3-		H	H	H	H
A391	CH3-		H	H	H	H
A392	CH3-		H	H	H	H
A393	CH3-		H	H	H	H
A394	CH3-		H	H	H	H
A395	CH3-		H	H	H	H
A396	CH3-		H	H	H	H
A397	CH3-		H	H	H	H
A398	CH3-		H	H	H	H
A399	CH3-		H	H	H	H

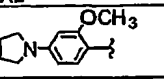
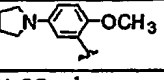
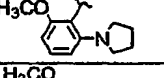
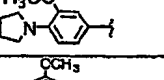
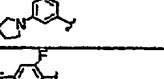
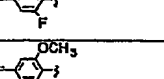
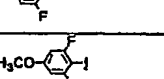
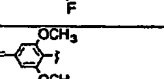
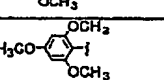
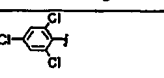
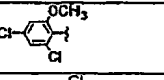
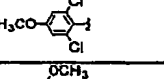
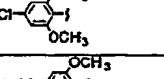
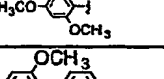
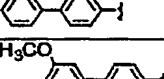
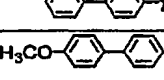
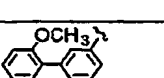
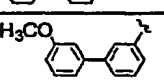
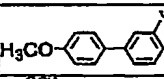
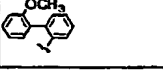


No.	R1	R2	R3	R4	R5	R6
A400	CH ₃ -		H	H	H	H
A401	CH ₃ -		H	H	H	H
A402	CH ₃ -		H	H	H	H
A403	CH ₃ -		H	H	H	H
A404	CH ₃ -		H	H	H	H
A405	CH ₃ -		H	H	H	H
A406	CH ₃ -		H	H	H	H
A407	CH ₃ -		H	H	H	H
A408	CH ₃ -		H	H	H	H
A409	CH ₃ -		H	H	H	H
A410	CH ₃ -		H	H	H	H
A411	CH ₃ -		H	H	H	H
A412	CH ₃ -		H	H	H	H
A413	CH ₃ -		H	H	H	H
A414	CH ₃ -		H	H	H	H
A415	CH ₃ -		H	H	H	H
A416	CH ₃ -		H	H	H	H
A417	CH ₃ -		H	H	H	H
A418	CH ₃ -		H	H	H	H
A419	CH ₃ -		H	H	H	H
A420	CH ₃ -		H	H	H	H
A421	CH ₃ -		H	H	H	H

No.	R1	R2	R3	R4	R5	R6
A422	CH3-		H	H	H	H
A423	CH3-		H	H	H	H
A424	CH3-		H	H	H	H
A425	CH3-		H	H	H	H
A426	CH3-		H	H	H	H
A427	CH3-		H	H	H	H
A428	CH3-		H	H	H	H
A429	CH3-		H	H	H	H
A430	CH3-		H	H	H	H
A431	CH3-		H	H	H	H
A432	CH3-		H	H	H	H
A433	CH3-		H	H	H	H
A434	CH3-		H	H	H	H
A435	CH3-		H	H	H	H
A436	CH3-		H	H	H	H
A437	CH3-		H	H	H	H
A438	CH3-		H	H	H	H
A439	CH3-		H	H	H	H
A440	CH3-		H	H	H	H
A441	CH3-		H	H	H	H
A442	CH3-		H	H	H	H
A443	CH3-		H	H	H	H























No.	R1	R2	R3	R4	R5	R6
A444	CH3-		H	H	H	H
A445	CH3-		H	H	H	H
A446	CH3-		H	H	H	H
A447	CH3-		H	H	H	H
A448	CH3-		H	H	H	H
A449	CH3-		H	H	H	H
A450	CH3-		H	H	H	H
A451	CH3-		H	H	H	H
A452	CH3-		H	H	H	H
A453	CH3-		H	H	H	H
A454	CH3-		H	H	H	H
A455	CH3-		H	H	H	H
A456	CH3-		H	H	H	H
A457	CH3-		H	H	H	H
A458	CH3-		H	H	H	H
A459	CH3-		H	H	H	H
A460	CH3-		H	H	H	H
A461	CH3-		H	H	H	H
A462	CH3-		H	H	H	H
A463	CH3-		H	H	H	H
A464	CH3-		H	H	H	H
A465	CH3-		H	H	H	H

No.	R1	R2	R3	R4	R5	R6
A466	CH3-		H	H	H	H
A467	CH3-		H	H	H	H
A468	CH3-		H	H	H	H
A469	CH3-		H	H	H	H
A470	CH3-		H	H	H	H
A471	CH3-		H	H	H	H
A472	CH3-		H	H	H	H
A473	CH3-		H	H	H	H
A474	CH3-		H	H	H	H
A475	CH3-		H	H	H	H
A476	CH3-		H	H	H	H
A477	CH3-		H	H	H	H
A478	CH3-		H	H	H	H
A479	CH3-		H	H	H	H
A480	CH3-		H	H	H	H
A481	CH3-		H	H	H	H
A482	CH3-		H	H	H	H
A483	CH3-		H	H	H	H
A484	CH3-		H	H	H	H
A485	CH3-		H	H	H	H
A486	CH3-		H	H	H	H
A487	CH3-		H	H	H	H

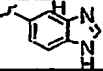
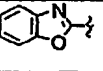
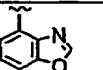
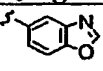
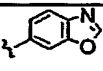
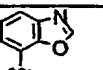
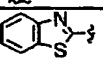
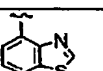
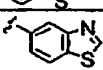
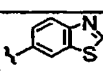
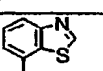
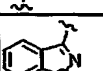
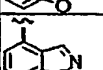
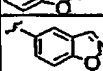
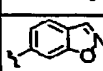
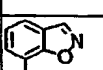
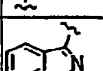
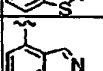
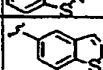
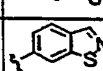
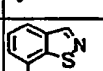
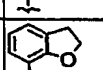
No.	R1	R2	R3	R4	R5	R6
A488	CH3-		H	H	H	H
A489	CH3-		H	H	H	H
A490	CH3-		H	H	H	H
A491	CH3-		H	H	H	H
A492	CH3-		H	H	H	H
A493	CH3-		H	H	H	H
A494	CH3-		H	H	H	H
A495	CH3-		H	H	H	H
A496	CH3-		H	H	H	H
A497	CH3-		H	H	H	H
A498	CH3-		H	H	H	H
A499	CH3-		H	H	H	H
A500	CH3-		H	H	H	H
A501	CH3-		H	H	H	H
A502	CH3-		H	H	H	H
A503	CH3-		H	H	H	H
A504	CH3-		H	H	H	H
A505	CH3-		H	H	H	H
A506	CH3-		H	H	H	H
A507	CH3-		H	H	H	H
A508	CH3-		H	H	H	H
A509	CH3-		H	H	H	H




















No.	R1	R2	R3	R4	R5	R6
A510	CH3-		H	H	H	H
A511	CH3-		H	H	H	H
A512	CH3-		H	H	H	H
A513	CH3-		H	H	H	H
A514	CH3-		H	H	H	H
A515	CH3-		H	H	H	H
A516	CH3-		H	H	H	H
A517	CH3-		H	H	H	H
A518	CH3-		H	H	H	H
A519	CH3-		H	H	H	H
A520	CH3-		H	H	H	H
A521	CH3-		H	H	H	H
A522	CH3-		H	H	H	H
A523	CH3-		H	H	H	H
A524	CH3-		H	H	H	H
A525	CH3-		H	H	H	H
A526	CH3-		H	H	H	H
A527	CH3-		H	H	H	H
A528	CH3-		H	H	H	H
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A530	CH3-		H	H	H	H
A531	CH3-		H	H	H	H

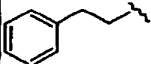
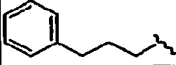



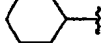







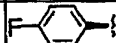
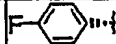

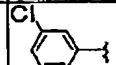
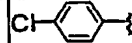



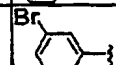
No.	R1	R2	R3	R4	R5	R6
A532	CH3-		H	H	H	H
A533	CH3-		H	H	H	H
A534	CH3-		H	H	H	H
A535	CH3-		H	H	H	H
A536	CH3-		H	H	H	H
A537	CH3-		H	H	H	H
A538	CH3-		H	H	H	H
A539	CH3-		H	H	H	H
A540	CH3-		H	H	H	H
A541	CH3-		H	H	H	H
A542	CH3-		H	H	H	H
A543	CH3-		H	H	H	H
A544	CH3-		H	H	H	H
A545	CH3-		H	H	H	H
A546	CH3-		H	H	H	H
A547	CH3-		H	H	H	H
A548	CH3-		H	H	H	H
A549	CH3-		H	H	H	H
A550	CH3-		H	H	H	H
A551	CH3-		H	H	H	H
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A553	CH3-		H	H	H	H

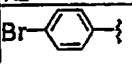
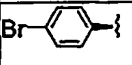
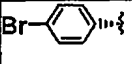
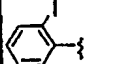
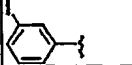
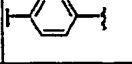
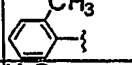
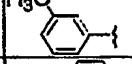
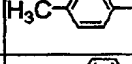
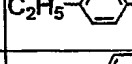
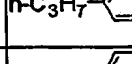
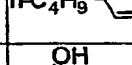
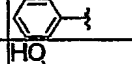
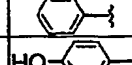
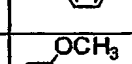
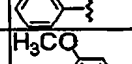
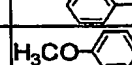
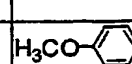
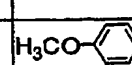
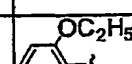
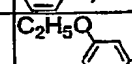
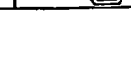
No.	R1	R2	R3	R4	R5	R6
A554	CH3-		H	H	H	H
A555	CH3-		H	H	H	H
A556	CH3-		H	H	H	H
A557	CH3-		H	H	H	H
A558	CH3-		H	H	H	H
A559	CH3-		H	H	H	H
A560	CH3-		H	H	H	H
A561	CH3-		H	H	H	H
A562	CH3-		H	H	H	H
A563	CH3-		H	H	H	H
A564	CH3-		H	H	H	H
A565	CH3-		H	H	H	H
A566	CH3-		H	H	H	H
A567	CH3-		H	H	H	H
A568	CH3-		H	H	H	H
A569	CH3-		H	H	H	H
A570	CH3-		H	H	H	H
A571	CH3-		H	H	H	H
A572	CH3-		H	H	H	H
A573	CH3-		H	H	H	H
A574	CH3-		H	H	H	H
A575	CH3-		H	H	H	H

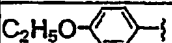
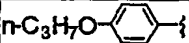
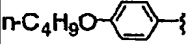
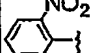
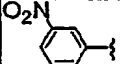
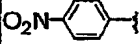
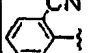
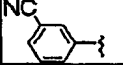

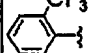
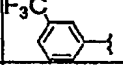
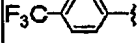
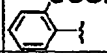
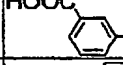
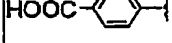
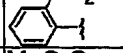
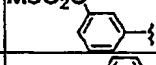
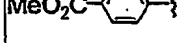

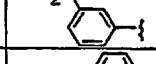

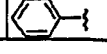
No.	R1	R2	R3	R4	R5	R6
A576	CH3-		H	H	H	H
A577	CH3-		H	H	H	H
A578	CH3-		H	H	H	H
A579	CH3-		H	H	H	H
A580	CH3-		H	H	H	H
A581	CH3-		H	H	H	H
A582	CH3-		H	H	H	H
A583	CH3-		H	H	H	H
A584	CH3-		H	H	H	H
A585	CH3-		H	H	H	H
A586	CH3-		H	H	H	H
A587	CH3-		H	H	H	H
A588	CH3-		H	H	H	H
A589	CH3-		H	H	H	H
A590	CH3-		H	H	H	H
A591	CH3-		H	H	H	H
A592	CH3-		H	H	H	H
A593	CH3-		H	H	H	H
A594	CH3-		H	H	H	H
A595	CH3-		H	H	H	H
A596	CH3-		H	H	H	H
A597	CH3-		H	H	H	H

No.	R1	R2	R3	R4	R5	R6
A598	CH3-		H	H	H	H
A599	CH3-		H	H	H	H
A600	CH3-		H	H	H	H
A601	CH3-		H	H	H	H
A602	CH3-		H	H	H	H
A603	CH3-		H	H	H	H
A604	CH3-		H	H	H	H
A605	CH3-		H	H	H	H
A606	CH3-		H	H	H	H
A607	CH3-		H	H	H	H
A608	CH3-		H	H	H	H
A609	CH3-		H	H	H	H
A610	CH3-		H	H	H	H
A611	CH3-		H	H	H	H
A612	CH3-		H	H	H	H
A613	CH3-		H	H	H	H
A614	CH3-		H	H	H	H
A615	CH3-		H	H	H	H
A616	CH3-		H	H	H	H
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A618	CH3-		H	H	H	H
A619	CH3-		H	H	H	H

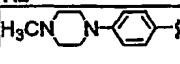
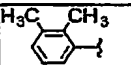
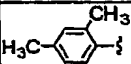
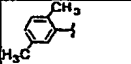
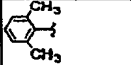
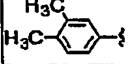
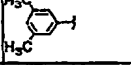
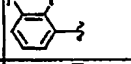
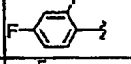
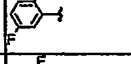
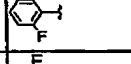
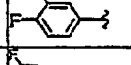
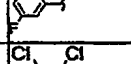
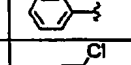
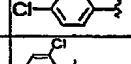
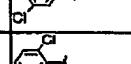
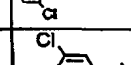
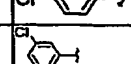
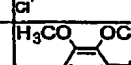
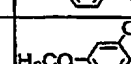
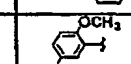
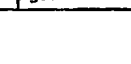
No.	R1	R2	R3	R4	R5	R6
A620	CH3-		H	H	H	H
A621	CH3-		H	H	H	H
A622	CH3-		H	H	H	H
A623	CH3-	CH3-	H	CH3	H	H
A624	CH3-	CH3CH2-	H	CH3	H	H
A625	CH3-		H	CH3	H	H
A626	CH3-		H	CH3	H	H
A627	CH3-		H	CH3	H	H
A628	CH3-		H	CH3	H	H
A629	CH3-		H	CH3	H	H
A630	CH3-		H	CH3	H	H
A631	CH3-		H	CH3	H	H
A632	CH3-		H	CH3	H	H
A633	CH3-		H	CH3	H	H
A634	CH3-		H	CH3	H	H
A635	CH3-		H	CH3	H	H
A636	CH3-		H	CH3	H	H
A637	CH3-		H	CH3	H	H
A638	CH3-		H	CH3	H	H
A639	CH3-	n-C8H17-	H	CH3	H	H
A640	CH3-		H	CH3	H	H
A641	CH3-		H	CH3	H	H

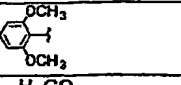
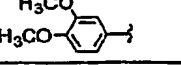
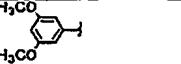
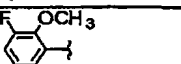
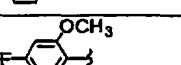
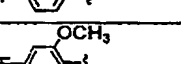
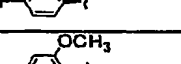
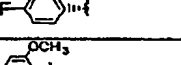
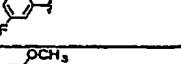

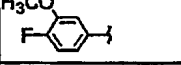
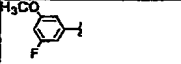
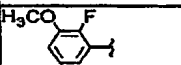
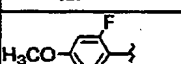
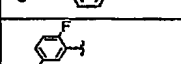
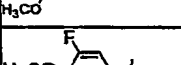
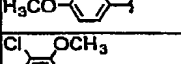
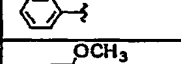
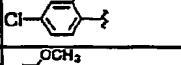
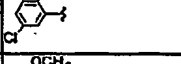

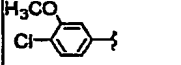
No.	R1	R2	R3	R4	R5	R6
A642	CH3-		H	CH3	H	H
A643	CH3-		H	CH3	H	H
A644	CH3-		H	CH3	H	H
A645	CH3-		H	CH3	H	H
A646	CH3-		H	CH3	H	H
A647	CH3-		H	CH3	H	H
A648	CH3-		H	CH3	H	H
A649	CH3-		H	CH3	H	H
A650	CH3-		H	CH3	H	H
A651	CH3-		H	CH3	H	H
A652	CH3-		H	CH3	H	H
A653	CH3-		H	CH3	H	H
A654	CH3-		H	CH3	H	H
A655	CH3-		H	CH3	H	H
A658	CH3-		H	CH3	H	H
A657	CH3-		H	CH3	H	H
A658	CH3-		H	CH3	H	H
A659	CH3-		H	CH3	H	H
A660	CH3-		H	CH3	H	H
A661	CH3-		H	CH3	H	H
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A663	CH3-		H	CH3	H	H

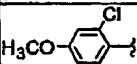

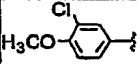

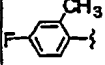


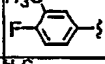

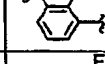
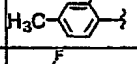

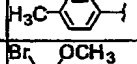
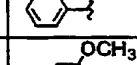
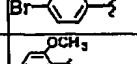


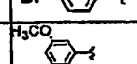

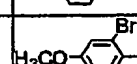
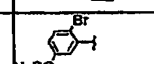

No.	R1	R2	R3	R4	R5	R6
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A665	CH3-		H	CH3	H	H
A666	CH3-		H	CH3	H	H
A667	CH3-		H	CH3	H	H
A668	CH3-		H	CH3	H	H
A669	CH3-		H	CH3	H	H
A670	CH3-		H	CH3	H	H
A671	CH3-		H	CH3	H	H
A672	CH3-		H	CH3	H	H
A673	CH3-		H	CH3	H	H
A674	CH3-		H	CH3	H	H
A675	CH3-		H	CH3	H	H
A676	CH3-		H	CH3	H	H
A677	CH3-		H	CH3	H	H
A678	CH3-		H	CH3	H	H
A679	CH3-		H	CH3	H	H
A680	CH3-		H	CH3	H	H
A681	CH3-		H	CH3	H	H
A682	CH3-		H	CH3	H	H
A683	CH3-		H	CH3	H	H
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A685	CH3-		H	CH3	H	H

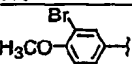
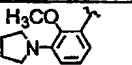
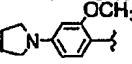
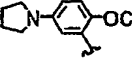
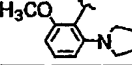
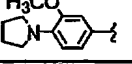
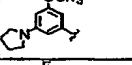
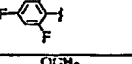
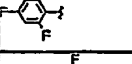
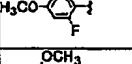
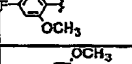
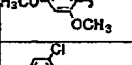
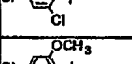
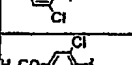
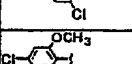
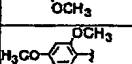
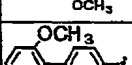
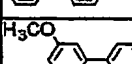
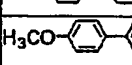
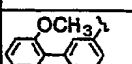
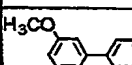
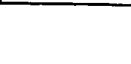
No.	R1	R2	R3	R4	R5	R6
A686	CH ₃ -		H	CH ₃	H	H
A687	CH ₃ -		H	CH ₃	H	H
A688	CH ₃ -		H	CH ₃	H	H
A689	CH ₃ -		H	CH ₃	H	H
A690	CH ₃ -		H	CH ₃	H	H
A691	CH ₃ -		H	CH ₃	H	H
A692	CH ₃ -		H	CH ₃	H	H
A693	CH ₃ -		H	CH ₃	H	H
A694	CH ₃ -		H	CH ₃	H	H
A695	CH ₃ -		H	CH ₃	H	H
A696	CH ₃ -		H	CH ₃	H	H
A697	CH ₃ -		H	CH ₃	H	H
A698	CH ₃ -		H	CH ₃	H	H
A699	CH ₃ -		H	CH ₃	H	H
A700	CH ₃ -		H	CH ₃	H	H
A701	CH ₃ -		H	CH ₃	H	H
A702	CH ₃ -		H	CH ₃	H	H
A703	CH ₃ -		H	CH ₃	H	H
A704	CH ₃ -		H	CH ₃	H	H
A705	CH ₃ -		H	CH ₃	H	H
A706	CH ₃ -		H	CH ₃	H	H
A707	CH ₃ -		H	CH ₃	H	H

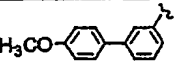

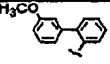
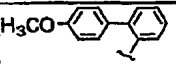
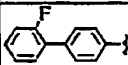
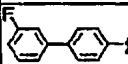
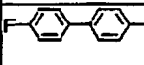
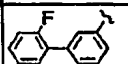
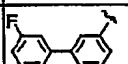
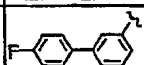


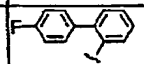

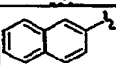


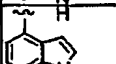
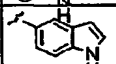


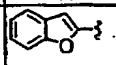
No.	R1	R2	R3	R4	R5	R6
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A709	CH3-		H	CH3	H	H
A710	CH3-		H	CH3	H	H
A711	CH3-		H	CH3	H	H
A712	CH3-		H	CH3	H	H
A713	CH3-		H	CH3	H	H
A714	CH3-		H	CH3	H	H
A715	CH3-		H	CH3	H	H
A716	CH3-		H	CH3	H	H
A717	CH3-		H	CH3	H	H
A718	CH3-		H	CH3	H	H
A719	CH3-		H	CH3	H	H
A720	CH3-		H	CH3	H	H
A721	CH3-		H	CH3	H	H
A722	CH3-		H	CH3	H	H
A723	CH3-		H	CH3	H	H
A724	CH3-		H	CH3	H	H
A725	CH3-		H	CH3	H	H
A726	CH3-		H	CH3	H	H
A727	CH3-		H	CH3	H	H
A728	CH3-		H	CH3	H	H
A729	CH3-		H	CH3	H	H

No.	R1	R2	R3	R4	R5	R6
A730	CH3-		H	CH3	H	H
A731	CH3-		H	CH3	H	H
A732	CH3-		H	CH3	H	H
A733	CH3-		H	CH3	H	H
A734	CH3-		H	CH3	H	H
A735	CH3-		H	CH3	H	H
A736	CH3-		H	CH3	H	H
A737	CH3-		H	CH3	H	H
A738	CH3-		H	CH3	H	H
A739	CH3-		H	CH3	H	H
A740	CH3-		H	CH3	H	H
A741	CH3-		H	CH3	H	H
A742	CH3-		H	CH3	H	H
A743	CH3-		H	CH3	H	H
A744	CH3-		H	CH3	H	H
A745	CH3-		H	CH3	H	H
A746	CH3-		H	CH3	H	H
A747	CH3-		H	CH3	H	H
A748	CH3-		H	CH3	H	H
A749	CH3-		H	CH3	H	H
A750	CH3-		H	CH3	H	H
A751	CH3-		H	CH3	H	H

No.	R1	R2	R3	R4	R5	R6
A752	CH3-		H	CH3	H	H
A753	CH3-		H	CH3	H	H
A754	CH3-		H	CH3	H	H
A755	CH3-		H	CH3	H	H
A756	CH3-		H	CH3	H	H
A757	CH3-		H	CH3	H	H
A758	CH3-		H	CH3	H	H
A759	CH3-		H	CH3	H	H
A760	CH3-		H	CH3	H	H
A761	CH3-		H	CH3	H	H
A762	CH3-		H	CH3	H	H
A763	CH3-		H	CH3	H	H
A764	CH3-		H	CH3	H	H
A765	CH3-		H	CH3	H	H
A766	CH3-		H	CH3	H	H
A767	CH3-		H	CH3	H	H
A768	CH3-		H	CH3	H	H
A769	CH3-		H	CH3	H	H
A770	CH3-		H	CH3	H	H
A771	CH3-		H	CH3	H	H
A772	CH3-		H	CH3	H	H
A773	CH3-		H	CH3	H	H

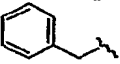
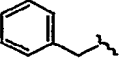

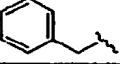

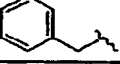

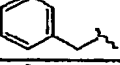

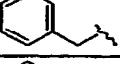

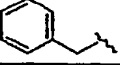

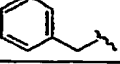

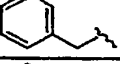

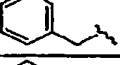

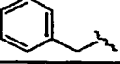

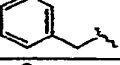

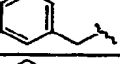

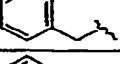

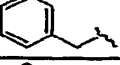

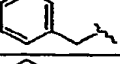
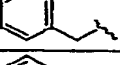

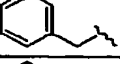
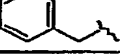
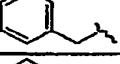
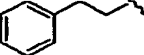
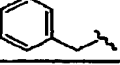
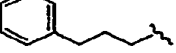
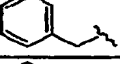

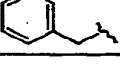
No.	R1	R2	R3	R4	R5	R6
A774	CH3-		H	CH3	H	H
A775	CH3-		H	CH3	H	H
A776	CH3-		H	CH3	H	H
A777	CH3-		H	CH3	H	H
A778	CH3-		H	CH3	H	H
A779	CH3-		H	CH3	H	H
A780	CH3-		H	CH3	H	H
A781	CH3-		H	CH3	H	H
A782	CH3-		H	CH3	H	H
A783	CH3-		H	CH3	H	H
A784	CH3-		H	CH3	H	H
A785	CH3-		H	CH3	H	H
A786	CH3-		H	CH3	H	H
A787	CH3-		H	CH3	H	H
A788	CH3-		H	CH3	H	H
A789	CH3-		H	CH3	H	H
A790	CH3-		H	CH3	H	H
A791	CH3-		H	CH3	H	H
A792	CH3-		H	CH3	H	H
A793	CH3-		H	CH3	H	H
A794	CH3-		H	CH3	H	H
A795	CH3-		H	CH3	H	H


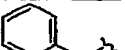

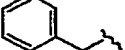

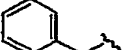
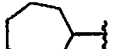








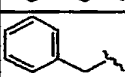

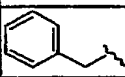







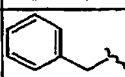

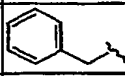

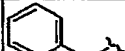





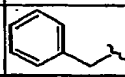

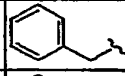

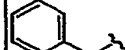

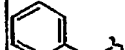


No.	R1	R2	R3	R4	R5	R6
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A797	CH3-		H	CH3	H	H
A798	CH3-		H	CH3	H	H
A799	CH3-		H	CH3	H	H
A800	CH3-		H	CH3	H	H
A801	CH3-		H	CH3	H	H
A802	CH3-		H	CH3	H	H
A803	CH3-		H	CH3	H	H
A804	CH3-		H	CH3	H	H
A805	CH3-		H	CH3	H	H
A806	CH3-		H	CH3	H	H
A807	CH3-		H	CH3	H	H
A808	CH3-		H	CH3	H	H
A809	CH3-		H	CH3	H	H
A810	CH3-		H	CH3	H	H
A811	CH3-		H	CH3	H	H
A812	CH3-		H	CH3	H	H
A813	CH3-		H	CH3	H	H
A814	CH3-		H	CH3	H	H
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
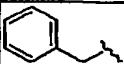

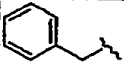

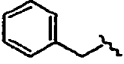

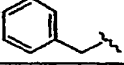

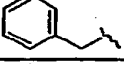

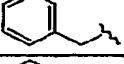

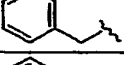

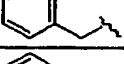

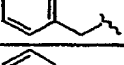

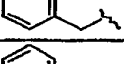

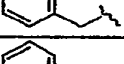

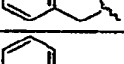







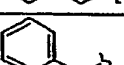

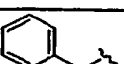

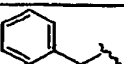

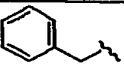

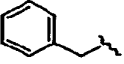

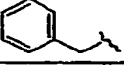


No.	R1	R2	R3	R4	R5	R6
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A819	CH3-		H	CH3	H	H
A820	CH3-		H	CH3	H	H
A821	CH3-		H	CH3	H	H
A822	CH3-		H	CH3	H	H
A823	CH3-		H	CH3	H	H
A824	CH3-		H	CH3	H	H
A825	CH3-		H	CH3	H	H
A826	CH3-		H	CH3	H	H
A827	CH3-		H	CH3	H	H
A828	CH3-		H	CH3	H	H
A829	CH3-		H	CH3	H	H
A830	CH3-		H	CH3	H	H
A831	CH3-		H	CH3	H	H
A832	CH3-		H	CH3	H	H
A833	CH3-		H	CH3	H	H
A834	CH3-		H	CH3	H	H
A835	CH3-		H	CH3	H	H
A836	CH3-		H	CH3	H	H
A837	CH3-		H	CH3	H	H
A838	CH3-		H	CH3	H	H
A839	CH3-		H	CH3	H	H

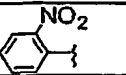
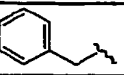
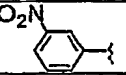
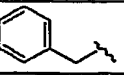
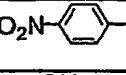
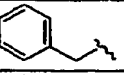
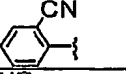
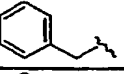
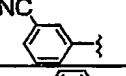
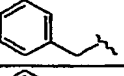
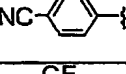
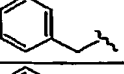
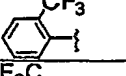
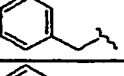
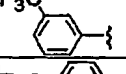
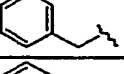
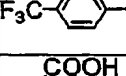
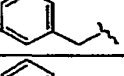
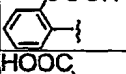
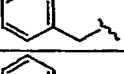
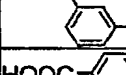
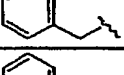
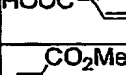
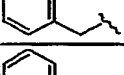
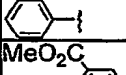
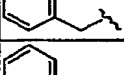
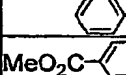
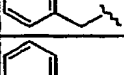
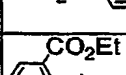
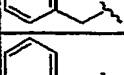
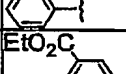
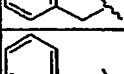
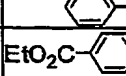
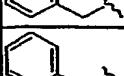
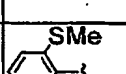
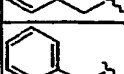

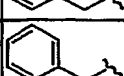
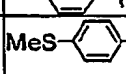
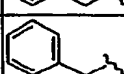
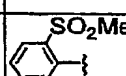
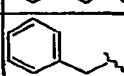
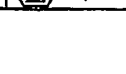

No.	R1	R2	R3	R4	R5	R6
A840	CH3-		H	CH3	H	H
A841	CH3-		H	CH3	H	H
A842	CH3-		H	CH3	H	H
A843	CH3-		H	CH3	H	H
A844	CH3-		H	CH3	H	H
A845	CH3-		H	CH3	H	H
A846	CH3-		H	CH3	H	H
A847	CH3-		H	CH3	H	H
A848	CH3-		H	CH3	H	H
A849	CH3-		H	CH3	H	H
A850	CH3-		H	CH3	H	H
A851	CH3-		H	CH3	H	H
A852	CH3-		H	CH3	H	H
A853	CH3-		H	CH3	H	H
A854	CH3-		H	CH3	H	H
A855	CH3-		H	CH3	H	H
A856	CH3-		H	CH3	H	H
A857	CH3-		H	CH3	H	H
A858	CH3-		H	CH3	H	H
A859	CH3-		H	CH3	H	H
A860	CH3-		H	CH3	H	H

No.	R1	R2	R3	R4	R5	R6
A861	CH3-		H	CH3	H	H
A862	CH3-		H	CH3	H	H
A863	CH3-		H	CH3	H	H
A864	CH3-		H	CH3	H	H
A865	CH3-		H	CH3	H	H
A866	CH3-		H	CH3	H	H
A867	CH3-		H	CH3	H	H
A868	CH3-		H	CH3	H	H
A869	CH3-		H	CH3	H	H
A870	CH3-		H	CH3	H	H
A871	CH3-		H	CH3	H	H
A872	CH3-		H	CH3	H	H
A873	CH3-		H	CH3	H	H
A874	CH3-		H	CH3	H	H
A875	CH3-		H	CH3	H	H
A876	CH3-		H	CH3	H	H
A877	CH3-		H	CH3	H	H
A878	CH3-		H	CH3	H	H
A879	CH3-		H	CH3	H	H
A880	CH3-		H	CH3	H	H
A881	CH3-		H	CH3	H	H
A882	CH3-		H	CH3	H	H

No.	R1	R2	R3	R4	R5	R6
A883	CH ₃ -	CH ₃ -	H		H	H
A884	CH ₃ -	CH ₃ CH ₂ -	H		H	H
A885	CH ₃ -		H		H	H
A886	CH ₃ -		H		H	H
A887	CH ₃ -		H		H	H
A888	CH ₃ -		H		H	H
A889	CH ₃ -		H		H	H
A890	CH ₃ -		H		H	H
A891	CH ₃ -		H		H	H
A892	CH ₃ -		H		H	H
A893	CH ₃ -		H		H	H
A894	CH ₃ -		H		H	H
A895	CH ₃ -		H		H	H
A896	CH ₃ -		H		H	H
A897	CH ₃ -		H		H	H
A898	CH ₃ -		H		H	H
A899	CH ₃ -	n-C ₈ H ₁₇ -	H		H	H
A900	CH ₃ -		H		H	H
A901	CH ₃ -		H		H	H
A902	CH ₃ -		H		H	H
A903	CH ₃ -		H		H	H
A904	CH ₃ -		H		H	H

No.	R1	R2	R3	R4	R5	R6
A905	CH ₃ -		H		H	H
A906	CH ₃ -		H		H	H
A907	CH ₃ -		H		H	H
A908	CH ₃ -		H		H	H
A909	CH ₃ -		H		H	H
A910	CH ₃ -		H		H	H
A911	CH ₃ -		H		H	H
A912	CH ₃ -		H		H	H
A913	CH ₃ -		H		H	H
A914	CH ₃ -		H		H	H
A915	CH ₃ -		H		H	H
A916	CH ₃ -		H		H	H
A917	CH ₃ -		H		H	H
A918	CH ₃ -		H		H	H
A919	CH ₃ -		H		H	H
A920	CH ₃ -		H		H	H
A921	CH ₃ -		H		H	H
A922	CH ₃ -		H		H	H
A923	CH ₃ -		H		H	H
A924	CH ₃ -		H		H	H
A925	CH ₃ -		H		H	H
A926	CH ₃ -		H		H	H

No.	R1	R2	R3	R4	R5	R6
A927	CH ₃ -		H		H	H
A928	CH ₃ -		H		H	H
A929	CH ₃ -		H		H	H
A930	CH ₃ -		H		H	H
A931	CH ₃ -		H		H	H
A932	CH ₃ -		H		H	H
A933	CH ₃ -		H		H	H
A934	CH ₃ -		H		H	H
A935	CH ₃ -		H		H	H
A936	CH ₃ -		H		H	H
A937	CH ₃ -		H		H	H
A938	CH ₃ -		H		H	H
A939	CH ₃ -		H		H	H
A940	CH ₃ -		H		H	H
A941	CH ₃ -		H		H	H
A942	CH ₃ -		H		H	H
A943	CH ₃ -		H		H	H
A944	CH ₃ -		H		H	H
A945	CH ₃ -		H		H	H
A946	CH ₃ -		H		H	H
A947	CH ₃ -		H		H	H
A948	CH ₃ -		H		H	H

No.	R1	R2	R3	R4	R5	R6
A949	CH3-		H		H	H
A950	CH3-		H		H	H
A951	CH3-		H		H	H
A952	CH3-		H		H	H
A953	CH3-		H		H	H
A954	CH3-		H		H	H
A955	CH3-		H		H	H
A956	CH3-		H		H	H
A957	CH3-		H		H	H
A958	CH3-		H		H	H
A959	CH3-		H		H	H
A960	CH3-		H		H	H
A961	CH3-		H		H	H
A962	CH3-		H		H	H
A963	CH3-		H		H	H
A964	CH3-		H		H	H
A965	CH3-		H		H	H
A966	CH3-		H		H	H
A967	CH3-		H		H	H
A968	CH3-		H		H	H
A969	CH3-		H		H	H
A970	CH3-		H		H	H

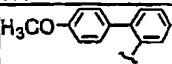
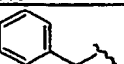
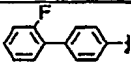
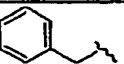
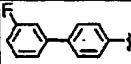
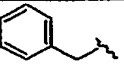
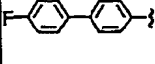
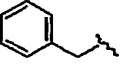
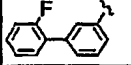
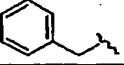
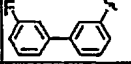
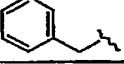
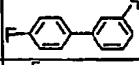
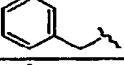

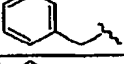

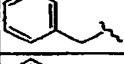

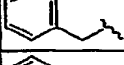

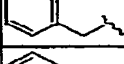
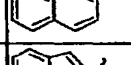
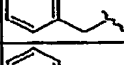
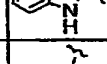
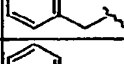
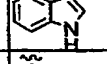
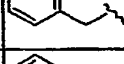
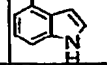
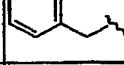
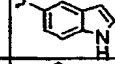
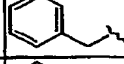
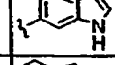
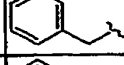
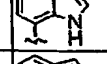
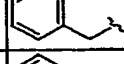
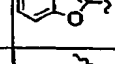
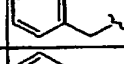
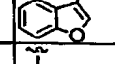
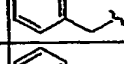
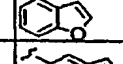
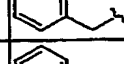
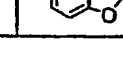
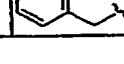
No.	R1	R2	R3	R4	R5	R6
A971	CH ₃ -		H		H	H
A972	CH ₃ -		H		H	H
A973	CH ₃ -		H		H	H
A974	CH ₃ -		H		H	H
A975	CH ₃ -		H		H	H
A976	CH ₃ -		H		H	H
A977	CH ₃ -		H		H	H
A978	CH ₃ -		H		H	H
A979	CH ₃ -		H		H	H
A980	CH ₃ -		H		H	H
A981	CH ₃ -		H		H	H
A982	CH ₃ -		H		H	H
A983	CH ₃ -		H		H	H
A984	CH ₃ -		H		H	H
A985	CH ₃ -		H		H	H
A986	CH ₃ -		H		H	H
A987	CH ₃ -		H		H	H
A988	CH ₃ -		H		H	H
A989	CH ₃ -		H		H	H
A990	CH ₃ -		H		H	H
A991	CH ₃ -		H		H	H
A992	CH ₃ -		H		H	H

No.	R1	R2	R3	R4	R5	R6
A993	CH3-		H		H	H
A994	CH3-		H		H	H
A995	CH3-		H		H	H
A996	CH3-		H		H	H
A997	CH3-		H		H	H
A998	CH3-		H		H	H
A999	CH3-		H		H	H
A1000	CH3-		H		H	H
A1001	CH3-		H		H	H
A1002	CH3-		H		H	H
A1003	CH3-		H		H	H
A1004	CH3-		H		H	H
A1005	CH3-		H		H	H
A1006	CH3-		H		H	H
A1007	CH3-		H		H	H
A1008	CH3-		H		H	H
A1009	CH3-		H		H	H
A1010	CH3-		H		H	H
A1011	CH3-		H		H	H
A1012	CH3-		H		H	H
A1013	CH3-		H		H	H
A1014	CH3-		H		H	H


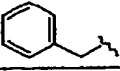

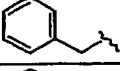

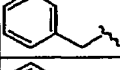

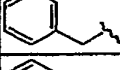

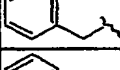

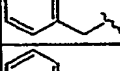

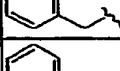

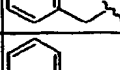

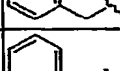

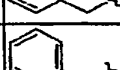

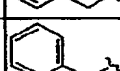

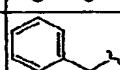

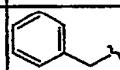

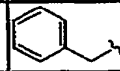

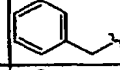

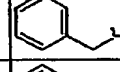

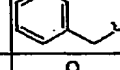

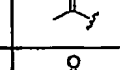






No.	R1	R2	R3	R4	R5	R6
A1015	CH3-		H		H	H
A1016	CH3-		H		H	H
A1017	CH3-		H		H	H
A1018	CH3-		H		H	H
A1019	CH3-		H		H	H
A1020	CH3-		H		H	H
A1021	CH3-		H		H	H
A1022	CH3-		H		H	H
A1023	CH3-		H		H	H
A1024	CH3-		H		H	H
A1025	CH3-		H		H	H
A1026	CH3-		H		H	H
A1027	CH3-		H		H	H
A1028	CH3-		H		H	H
A1029	CH3-		H		H	H
A1030	CH3-		H		H	H
A1031	CH3-		H		H	H
A1032	CH3-		H		H	H
A1033	CH3-		H		H	H
A1034	CH3-		H		H	H
A1035	CH3-		H		H	H
A1036	CH3-		H		H	H











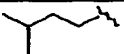







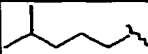

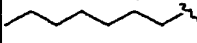




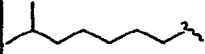

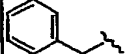

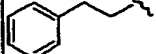

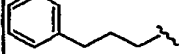







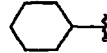

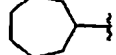

No.	R1	R2	R3	R4	R5	R6
A1037	CH3-		H		H	H
A1038	CH3-		H		H	H
A1039	CH3-		H		H	H
A1040	CH3-		H		H	H
A1041	CH3-		H		H	H
A1042	CH3-		H		H	H
A1043	CH3-		H		H	H
A1044	CH3-		H		H	H
A1045	CH3-		H		H	H
A1046	CH3-		H		H	H
A1047	CH3-		H		H	H
A1048	CH3-		H		H	H
A1049	CH3-		H		H	H
A1050	CH3-		H		H	H
A1051	CH3-		H		H	H
A1052	CH3-		H		H	H
A1053	CH3-		H		H	H
A1054	CH3-		H		H	H
A1055	CH3-		H		H	H
A1056	CH3-		H		H	H
A1057	CH3-		H		H	H
A1058	CH3-		H		H	H













































No.	R1	R2	R3	R4	R5	R6
A1059	CH ₃ -		H		H	H
A1060	CH ₃ -		H		H	H
A1061	CH ₃ -		H		H	H
A1062	CH ₃ -		H		H	H
A1063	CH ₃ -		H		H	H
A1064	CH ₃ -		H		H	H
A1065	CH ₃ -		H		H	H
A1066	CH ₃ -		H		H	H
A1067	CH ₃ -		H		H	H
A1068	CH ₃ -		H		H	H
A1069	CH ₃ -		H		H	H
A1070	CH ₃ -		H		H	H
A1071	CH ₃ -		H		H	H
A1072	CH ₃ -		H		H	H
A1073	CH ₃ -		H		H	H
A1074	CH ₃ -		H		H	H
A1075	CH ₃ -		H		H	H
A1076	CH ₃ -		H		H	H
A1077	CH ₃ -		H		H	H
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A1080	CH ₃ -		H		H	H

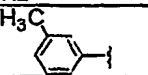

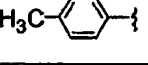

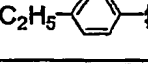

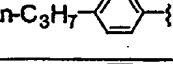

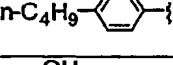

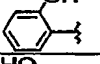

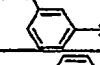

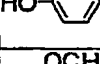

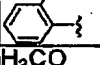

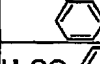

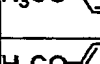

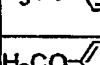

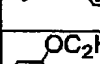

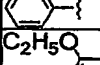

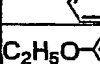

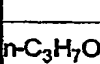

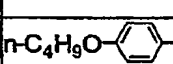

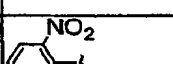

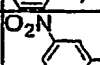

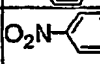

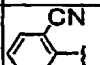



No.	R1	R2	R3	R4	R5	R6
A1081	CH ₃ -		H		H	H
A1082	CH ₃ -		H		H	H
A1083	CH ₃ -		H		H	H
A1084	CH ₃ -		H		H	H
A1085	CH ₃ -		H		H	H
A1086	CH ₃ -		H		H	H
A1087	CH ₃ -		H		H	H
A1088	CH ₃ -		H		H	H
A1089	CH ₃ -		H		H	H
A1090	CH ₃ -		H		H	H
A1091	CH ₃ -		H		H	H
A1092	CH ₃ -		H		H	H
A1093	CH ₃ -		H		H	H
A1094	CH ₃ -		H		H	H
A1095	CH ₃ -		H		H	H
A1096	CH ₃ -		H		H	H
A1097	CH ₃ -		H		H	H
A1098	CH ₃ -		H		H	H
A1099	CH ₃ -		H		H	H
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A1102	CH ₃ -		H		H	H

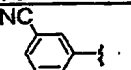

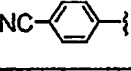

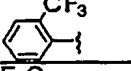

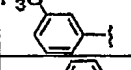

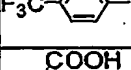

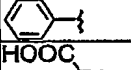

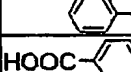

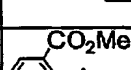

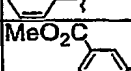

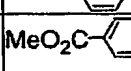

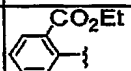

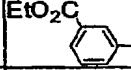

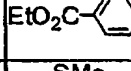

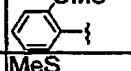

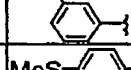

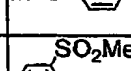

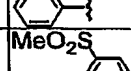

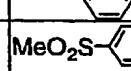

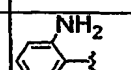

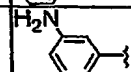





No.	R1	R2	R3	R4	R5	R6
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A1104	CH ₃ -		H		H	H
A1105	CH ₃ -		H		H	H
A1106	CH ₃ -		H		H	H
A1107	CH ₃ -		H		H	H
A1108	CH ₃ -		H		H	H
A1109	CH ₃ -		H		H	H
A1110	CH ₃ -		H		H	H
A1111	CH ₃ -		H		H	H
A1112	CH ₃ -		H		H	H
A1113	CH ₃ -		H		H	H
A1114	CH ₃ -		H		H	H
A1115	CH ₃ -		H		H	H
A1116	CH ₃ -		H		H	H
A1117	CH ₃ -		H		H	H
A1118	CH ₃ -		H		H	H
A1119	CH ₃ -		H		H	H
A1120	CH ₃ -		H		H	H
A1121	CH ₃ -		H		H	H
A1122	CH ₃ -		H		H	H
A1123	CH ₃ -		H		H	H
A1124	CH ₃ -		H		H	H

No.	R1	R2	R3	R4	R5	R6
A1125	CH3-		H		H	H
A1126	CH3-		H		H	H
A1127	CH3-		H		H	H
A1128	CH3-		H		H	H
A1129	CH3-		H		H	H
A1130	CH3-		H		H	H
A1131	CH3-		H		H	H
A1132	CH3-		H		H	H
A1133	CH3-		H		H	H
A1134	CH3-		H		H	H
A1135	CH3-		H		H	H
A1136	CH3-		H		H	H
A1137	CH3-		H		H	H
A1138	CH3-		H		H	H
A1139	CH3-		H		H	H
A1140	CH3-		H		H	H
A1141	CH3-		H		H	H
A1142	CH3-		H		H	H
A1143	CH3-	CH3-	H		H	H
A1144	CH3-	CH3CH2-	H		H	H
A1145	CH3-		H		H	H
A1146	CH3-		H		H	H













































No.	R1	R2	R3	R4	R5	R6
A1147	CH3-		H		H	H
A1148	CH3-		H		H	H
A1149	CH3-		H		H	H
A1150	CH3-		H		H	H
A1151	CH3-		H		H	H
A1152	CH3-		H		H	H
A1153	CH3-		H		H	H
A1154	CH3-		H		H	H
A1155	CH3-		H		H	H
A1156	CH3-		H		H	H
A1157	CH3-		H		H	H
A1158	CH3-		H		H	H
A1159	CH3-	n-C8H17-	H		H	H
A1160	CH3-		H		H	H
A1161	CH3-		H		H	H
A1162	CH3-		H		H	H
A1163	CH3-		H		H	H
A1164	CH3-		H		H	H
A1165	CH3-		H		H	H
A1166	CH3-		H		H	H
A1167	CH3-		H		H	H
A1168	CH3-		H		H	H

No.	R1	R2	R3	R4	R5	R6
A1169	CH3-		H		H	H
A1170	CH3-		H		H	H
A1171	CH3-		H		H	H
A1172	CH3-		H		H	H
A1173	CH3-		H		H	H
A1174	CH3-		H		H	H
A1175	CH3-		H		H	H
A1176	CH3-		H		H	H
A1177	CH3-		H		H	H
A1178	CH3-		H		H	H
A1179	CH3-		H		H	H
A1180	CH3-		H		H	H
A1181	CH3-		H		H	H
A1182	CH3-		H		H	H
A1183	CH3-		H		H	H
A1184	CH3-		H		H	H
A1185	CH3-		H		H	H
A1186	CH3-		H		H	H
A1187	CH3-		H		H	H
A1188	CH3-		H		H	H
A1189	CH3-		H		H	H
A1190	CH3-		H		H	H

No.	R1	R2	R3	R4	R5	R6
A1191	CH ₃ -		H		H	H
A1192	CH ₃ -		H		H	H
A1193	CH ₃ -		H		H	H
A1194	CH ₃ -		H		H	H
A1195	CH ₃ -		H		H	H
A1196	CH ₃ -		H		H	H
A1197	CH ₃ -		H		H	H
A1198	CH ₃ -		H		H	H
A1199	CH ₃ -		H		H	H
A1200	CH ₃ -		H		H	H
A1201	CH ₃ -		H		H	H
A1202	CH ₃ -		H		H	H
A1203	CH ₃ -		H		H	H
A1204	CH ₃ -		H		H	H
A1205	CH ₃ -		H		H	H
A1206	CH ₃ -		H		H	H
A1207	CH ₃ -		H		H	H
A1208	CH ₃ -		H		H	H
A1209	CH ₃ -		H		H	H
A1210	CH ₃ -		H		H	H
A1211	CH ₃ -		H		H	H
A1212	CH ₃ -		H		H	H

No.	R1	R2	R3	R4	R5	R6
A1213	CH ₃ -		H		H	H
A1214	CH ₃ -		H		H	H
A1215	CH ₃ -		H		H	H
A1216	CH ₃ -		H		H	H
A1217	CH ₃ -		H		H	H
A1218	CH ₃ -		H		H	H
A1219	CH ₃ -		H		H	H
A1220	CH ₃ -		H		H	H
A1221	CH ₃ -		H		H	H
A1222	CH ₃ -		H		H	H
A1223	CH ₃ -		H		H	H
A1224	CH ₃ -		H		H	H
A1225	CH ₃ -		H		H	H
A1226	CH ₃ -		H		H	H
A1227	CH ₃ -		H		H	H
A1228	CH ₃ -		H		H	H
A1229	CH ₃ -		H		H	H
A1230	CH ₃ -		H		H	H
A1231	CH ₃ -		H		H	H
A1232	CH ₃ -		H		H	H
A1233	CH ₃ -		H		H	H
A1234	CH ₃ -		H		H	H

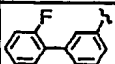

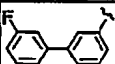

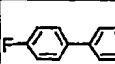

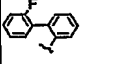

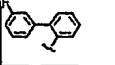

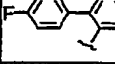

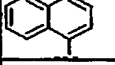

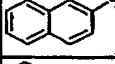

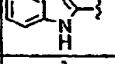

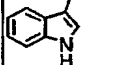

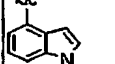

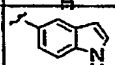

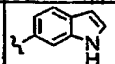

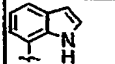

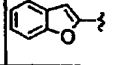

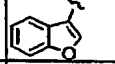

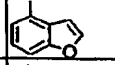

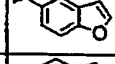

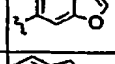

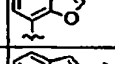

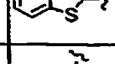

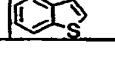

No.	R1	R2	R3	R4	R5	R6
A1235	CH ₃ -		H		H	H
A1236	CH ₃ -		H		H	H
A1237	CH ₃ -		H		H	H
A1238	CH ₃ -		H		H	H
A1239	CH ₃ -		H		H	H
A1240	CH ₃ -		H		H	H
A1241	CH ₃ -		H		H	H
A1242	CH ₃ -		H		H	H
A1243	CH ₃ -		H		H	H
A1244	CH ₃ -		H		H	H
A1245	CH ₃ -		H		H	H
A1246	CH ₃ -		H		H	H
A1247	CH ₃ -		H		H	H
A1248	CH ₃ -		H		H	H
A1249	CH ₃ -		H		H	H
A1250	CH ₃ -		H		H	H
A1251	CH ₃ -		H		H	H
A1252	CH ₃ -		H		H	H
A1253	CH ₃ -		H		H	H
A1254	CH ₃ -		H		H	H
A1255	CH ₃ -		H		H	H
A1256	CH ₃ -		H		H	H

No.	R1	R2	R3	R4	R5	R6
A1257	CH3-		H		H	H
A1258	CH3-		H		H	H
A1259	CH3-		H		H	H
A1260	CH3-		H		H	H
A1261	CH3-		H		H	H
A1262	CH3-		H		H	H
A1263	CH3-		H		H	H
A1264	CH3-		H		H	H
A1265	CH3-		H		H	H
A1266	CH3-		H		H	H
A1267	CH3-		H		H	H
A1268	CH3-		H		H	H
A1269	CH3-		H		H	H
A1270	CH3-		H		H	H
A1271	CH3-		H		H	H
A1272	CH3-		H		H	H
A1273	CH3-		H		H	H
A1274	CH3-		H		H	H
A1275	CH3-		H		H	H
A1276	CH3-		H		H	H
A1277	CH3-		H		H	H
A1278	CH3-		H		H	H

No.	R1	R2	R3	R4	R5	R6
A1279	CH3-		H		H	H
A1280	CH3-		H		H	H
A1281	CH3-		H		H	H
A1282	CH3-		H		H	H
A1283	CH3-		H		H	H
A1284	CH3-		H		H	H
A1285	CH3-		H		H	H
A1286	CH3-		H		H	H
A1287	CH3-		H		H	H
A1288	CH3-		H		H	H
A1289	CH3-		H		H	H
A1290	CH3-		H		H	H
A1291	CH3-		H		H	H
A1292	CH3-		H		H	H
A1293	CH3-		H		H	H
A1294	CH3-		H		H	H
A1295	CH3-		H		H	H
A1296	CH3-		H		H	H
A1297	CH3-		H		H	H
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A1299	CH3-		H		H	H
A1300	CH3-		H		H	H

















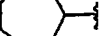




No.	R1	R2	R3	R4	R5	R6
A1301	CH3-		H		H	H
A1302	CH3-		H		H	H
A1303	CH3-		H		H	H
A1304	CH3-		H		H	H
A1305	CH3-		H		H	H
A1306	CH3-		H		H	H
A1307	CH3-		H		H	H
A1308	CH3-		H		H	H
A1309	CH3-		H		H	H
A1310	CH3-		H		H	H
A1311	CH3-		H		H	H
A1312	CH3-		H		H	H
A1313	CH3-		H		H	H
A1314	CH3-		H		H	H
A1315	CH3-		H		H	H
A1316	CH3-		H		H	H
A1317	CH3-		H		H	H
A1318	CH3-		H		H	H
A1319	CH3-		H		H	H
A1320	CH3-		H		H	H
A1321	CH3-		H		H	H
A1322	CH3-		H		H	H

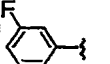



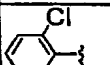



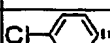
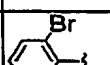
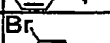

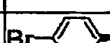

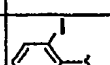


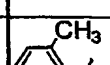
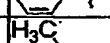
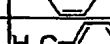
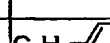
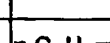
No.	R1	R2	R3	R4	R5	R6
A1323	CH3-		H		H	H
A1324	CH3-		H		H	H
A1325	CH3-		H		H	H
A1326	CH3-		H		H	H
A1327	CH3-		H		H	H
A1328	CH3-		H		H	H
A1329	CH3-		H		H	H
A1330	CH3-		H		H	H
A1331	CH3-		H		H	H
A1332	CH3-		H		H	H
A1333	CH3-		H		H	H
A1334	CH3-		H		H	H
A1335	CH3-		H		H	H
A1336	CH3-		H		H	H
A1337	CH3-		H		H	H
A1338	CH3-		H		H	H
A1339	CH3-		H		H	H
A1340	CH3-		H		H	H
A1341	CH3-		H		H	H
A1342	CH3-		H		H	H
A1343	CH3-		H		H	H
A1344	CH3-		H		H	H

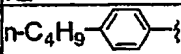

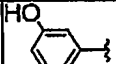
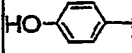
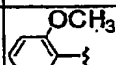
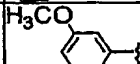
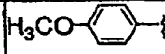
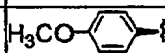
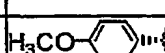
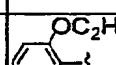
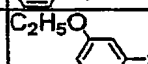
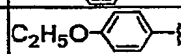
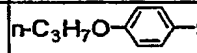
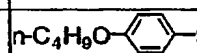

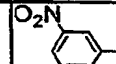
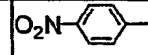

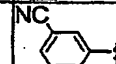
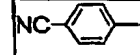

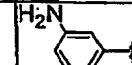
No.	R1	R2	R3	R4	R5	R6
A1345	CH3-		H		H	H
A1346	CH3-		H		H	H
A1347	CH3-		H		H	H
A1348	CH3-		H		H	H
A1349	CH3-		H		H	H
A1350	CH3-		H		H	H
A1351	CH3-		H		H	H
A1352	CH3-		H		H	H
A1353	CH3-		H		H	H
A1354	CH3-		H		H	H
A1355	CH3-		H		H	H
A1356	CH3-		H		H	H
A1357	CH3-		H		H	H
A1358	CH3-		H		H	H
A1359	CH3-		H		H	H
A1360	CH3-		H		H	H
A1361	CH3-		H		H	H
A1362	CH3-		H		H	H
A1363	CH3-		H		H	H
A1364	CH3-		H		H	H
A1365	CH3-		H		H	H
A1366	CH3-		H		H	H

No.	R1	R2	R3	R4	R5	R6
A1367	CH3-		H		H	H
A1368	CH3-		H		H	H
A1369	CH3-		H		H	H
A1370	CH3-		H		H	H
A1371	CH3-		H		H	H
A1372	CH3-		H		H	H
A1373	CH3-		H		H	H
A1374	CH3-		H		H	H
A1375	CH3-		H		H	H
A1376	CH3-		H		H	H
A1377	CH3-		H		H	H
A1378	CH3-		H		H	H
A1379	CH3-		H		H	H
A1380	CH3-		H		H	H
A1381	CH3-		H		H	H
A1382	CH3-		H		H	H
A1383	CH3-		H		H	H
A1384	CH3-		H		H	H
A1385	CH3-		H		H	H
A1386	CH3-		H		H	H
A1387	CH3-		H		H	H
A1388	CH3-		H		H	H








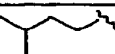





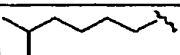

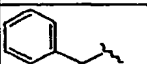
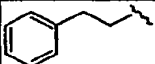
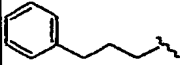


No.	R1	R2	R3	R4	R5	R6
A1389	CH3-		H		H	H
A1390	CH3-		H		H	H
A1391	CH3-		H		H	H
A1392	CH3-		H		H	H
A1393	CH3-		H		H	H
A1394	CH3-		H		H	H
A1395	CH3-		H		H	H
A1396	CH3-		H		H	H
A1397	CH3-		H		H	H
A1398	CH3-		H		H	H
A1399	CH3-		H		H	H
A1400	CH3-		H		H	H
A1401	CH3-		H		H	H
A1402	CH3-		H		H	H
A1403	CH3-	CH3-	CH3-	H	H	H
A1404	CH3-	CH3CH2-	CH3-	H	H	H
A1405	CH3-		CH3-	H	H	H
A1406	CH3-		CH3-	H	H	H
A1407	CH3-		CH3-	H	H	H
A1408	CH3-		CH3-	H	H	H
A1409	CH3-		CH3-	H	H	H
A1410	CH3-		CH3-	H	H	H



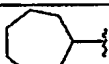



















No.	R1	R2	R3	R4	R5	R6
A1411	CH3-		CH3-	H	H	H
A1412	CH3-		CH3-	H	H	H
A1413	CH3-		CH3-	H	H	H
A1414	CH3-		CH3-	H	H	H
A1415	CH3-		CH3-	H	H	H
A1416	CH3-		CH3-	H	H	H
A1417	CH3-		CH3-	H	H	H
A1418	CH3-		CH3-	H	H	H
A1419	CH3-	n-C8H17-	CH3-	H	H	H
A1420	CH3-		CH3-	H	H	H
A1421	CH3-		CH3-	H	H	H
A1422	CH3-		CH3-	H	H	H
A1423	CH3-		CH3-	H	H	H
A1424	CH3-		CH3-	H	H	H
A1425	CH3-		CH3-	H	H	H
A1426	CH3-		CH3-	H	H	H
A1427	CH3-		CH3-	H	H	H
A1428	CH3-		CH3-	H	H	H
A1429	CH3-		CH3-	H	H	H
A1430	CH3-		CH3-	H	H	H
A1431	CH3-		CH3-	H	H	H
A1432	CH3-		CH3-	H	H	H























No.	R1	R2	R3	R4	R5	R6
A1433	CH ₃ -		CH ₃ -	H	H	H
A1434	CH ₃ -		CH ₃ -	H	H	H
A1435	CH ₃ -		CH ₃ -	H	H	H
A1436	CH ₃ -		CH ₃ -	H	H	H
A1437	CH ₃ -		CH ₃ -	H	H	H
A1438	CH ₃ -		CH ₃ -	H	H	H
A1439	CH ₃ -		CH ₃ -	H	H	H
A1440	CH ₃ -		CH ₃ -	H	H	H
A1441	CH ₃ -		CH ₃ -	H	H	H
A1442	CH ₃ -		CH ₃ -	H	H	H
A1443	CH ₃ -		CH ₃ -	H	H	H
A1444	CH ₃ -		CH ₃ -	H	H	H
A1445	CH ₃ -		CH ₃ -	H	H	H
A1446	CH ₃ -		CH ₃ -	H	H	H
A1447	CH ₃ -		CH ₃ -	H	H	H
A1448	CH ₃ -		CH ₃ -	H	H	H
A1449	CH ₃ -		CH ₃ -	H	H	H
A1450	CH ₃ -		CH ₃ -	H	H	H
A1451	CH ₃ -		CH ₃ -	H	H	H
A1452	CH ₃ -		CH ₃ -	H	H	H
A1453	CH ₃ -		CH ₃ -	H	H	H
A1454	CH ₃ -		CH ₃ -	H	H	H

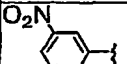
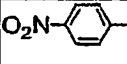
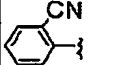
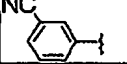
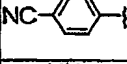
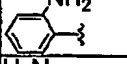
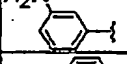
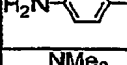
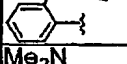
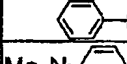
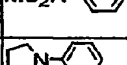
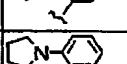
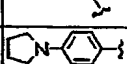
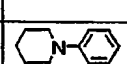
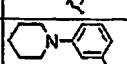
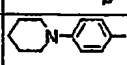
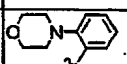
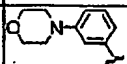
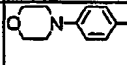
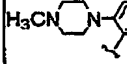
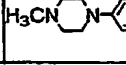

No.	R1	R2	R3	R4	R5	R6
A1455	CH3-		CH3-	H	H	H
A1456	CH3-		CH3-	H	H	H
A1457	CH3-		CH3-	H	H	H
A1458	CH3-		CH3-	H	H	H
A1459	CH3-		CH3-	H	H	H
A1460	CH3-		CH3-	H	H	H
A1461	CH3-		CH3-	H	H	H
A1462	CH3-		CH3-	H	H	H
A1463	CH3-		CH3-	H	H	H
A1464	CH3-		CH3-	H	H	H
A1465	CH3-		CH3-	H	H	H
A1466	CH3-		CH3-	H	H	H
A1467	CH3-		CH3-	H	H	H
A1468	CH3-		CH3-	H	H	H
A1469	CH3-		CH3-	H	H	H
A1470	CH3-		CH3-	H	H	H
A1471	CH3-		CH3-	H	H	H
A1472	CH3-		CH3-	H	H	H
A1473	CH3-		CH3-	H	H	H
A1474	CH3-		CH3-	H	H	H
A1475	CH3-		CH3-	H	H	H
A1476	CH3-		CH3-	H	H	H

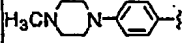
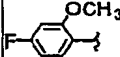
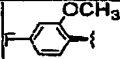
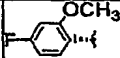

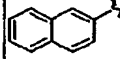
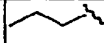


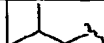
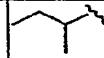


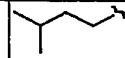
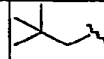
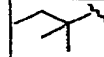

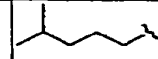


No.	R1	R2	R3	R4	R5	R6
A1477	CH3-		CH3-	H	H	H
A1478	CH3-		CH3-	H	H	H
A1479	CH3-		CH3-	H	H	H
A1480	CH3-		CH3-	H	H	H
A1481	CH3-		CH3-	H	H	H
A1482	CH3-		CH3-	H	H	H
A1483	CH3-		CH3-	H	H	H
A1484	CH3-		CH3-	H	H	H
A1485	CH3-		CH3-	H	H	H
A1486	CH3-		CH3-	H	H	H
A1487	CH3-		CH3-	H	H	H
A1488	CH3-		CH3-	H	H	H
A1489	CH3-		CH3-	H	H	H
A1490	CH3-		CH3-	H	H	H
A1491	CH3-		CH3-	H	H	H
A1492	CH3-		CH3-	H	H	H
A1493	CH3-		CH3-	H	H	H
A1494	CH3-		CH3-	H	H	H
A1495	CH3-		CH3-	H	H	H
A1496	CH3-		CH3-	H	H	H
A1497	CH3-		CH3-	H	H	H
A1498	CH3-	CH3-	H	H	CH3-	H

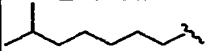
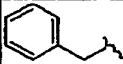
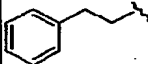
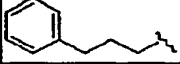



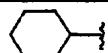
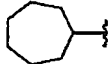




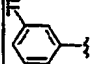
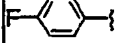



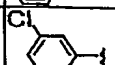
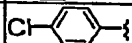
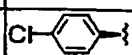
No.	R1	R2	R3	R4	R5	R6
A1499	CH3-	CH3CH2-	H	H	CH3-	H
A1500	CH3-		H	H	CH3-	H
A1501	CH3-		H	H	CH3-	H
A1502	CH3-		H	H	CH3-	H
A1503	CH3-		H	H	CH3-	H
A1504	CH3-		H	H	CH3-	H
A1505	CH3-		H	H	CH3-	H
A1506	CH3-		H	H	CH3-	H
A1507	CH3-		H	H	CH3-	H
A1508	CH3-		H	H	CH3-	H
A1509	CH3-		H	H	CH3-	H
A1510	CH3-		H	H	CH3-	H
A1511	CH3-		H	H	CH3-	H
A1512	CH3-		H	H	CH3-	H
A1513	CH3-		H	H	CH3-	H
A1514	CH3-	n-C8H17-	H	H	CH3-	H
A1515	CH3-		H	H	CH3-	H
A1516	CH3-		H	H	CH3-	H
A1517	CH3-		H	H	CH3-	H
A1518	CH3-		H	H	CH3-	H
A1519	CH3-		H	H	CH3-	H
A1520	CH3-		H	H	CH3-	H


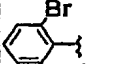
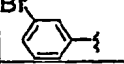
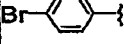
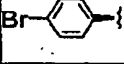
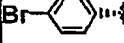
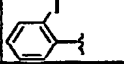
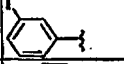
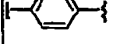
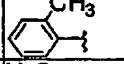
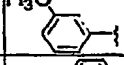
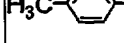
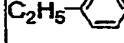
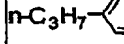
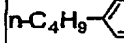
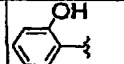
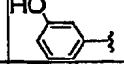
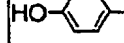
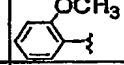
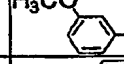
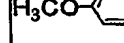
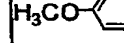
No.	R1	R2	R3	R4	R5	R6
A1521	CH3-		H	H	CH3-	H
A1522	CH3-		H	H	CH3-	H
A1523	CH3-		H	H	CH3-	H
A1524	CH3-		H	H	CH3-	H
A1525	CH3-		H	H	CH3-	H
A1526	CH3-		H	H	CH3-	H
A1527	CH3-		H	H	CH3-	H
A1528	CH3-		H	H	CH3-	H
A1529	CH3-		H	H	CH3-	H
A1530	CH3-		H	H	CH3-	H
A1531	CH3-		H	H	CH3-	H
A1532	CH3-		H	H	CH3-	H
A1533	CH3-		H	H	CH3-	H
A1534	CH3-		H	H	CH3-	H
A1535	CH3-		H	H	CH3-	H
A1536	CH3-		H	H	CH3-	H
A1537	CH3-		H	H	CH3-	H
A1538	CH3-		H	H	CH3-	H
A1539	CH3-		H	H	CH3-	H
A1540	CH3-		H	H	CH3-	H
A1541	CH3-		H	H	CH3-	H
A1542	CH3-		H	H	CH3-	H

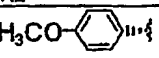
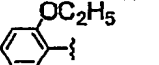
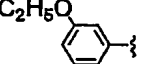
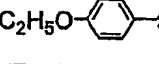
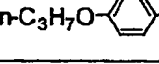
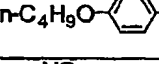
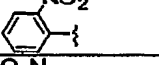
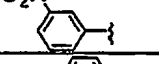
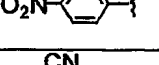
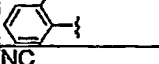
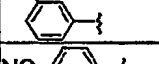
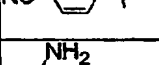
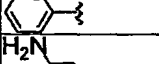
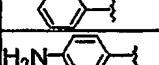
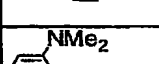
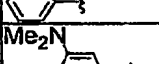
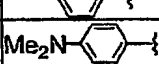
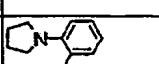
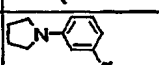
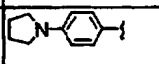
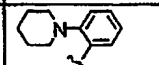

No.	R1	R2	R3	R4	R5	R6
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A1544	CH3-		H	H	CH3-	H
A1545	CH3-		H	H	CH3-	H
A1546	CH3-		H	H	CH3-	H
A1547	CH3-		H	H	CH3-	H
A1548	CH3-		H	H	CH3-	H
A1549	CH3-		H	H	CH3-	H
A1550	CH3-		H	H	CH3-	H
A1551	CH3-		H	H	CH3-	H
A1552	CH3-		H	H	CH3-	H
A1553	CH3-		H	H	CH3-	H
A1554	CH3-		H	H	CH3-	H
A1555	CH3-		H	H	CH3-	H
A1556	CH3-		H	H	CH3-	H
A1557	CH3-		H	H	CH3-	H
A1558	CH3-		H	H	CH3-	H
A1559	CH3-		H	H	CH3-	H
A1560	CH3-		H	H	CH3-	H
A1561	CH3-		H	H	CH3-	H
A1562	CH3-		H	H	CH3-	H
A1563	CH3-		H	H	CH3-	H
A1564	CH3-		H	H	CH3-	H

No.	R1	R2	R3	R4	R5	R6
A1565	CH3-		H	H	CH3-	H
A1566	CH3-		H	H	CH3-	H
A1567	CH3-		H	H	CH3-	H
A1568	CH3-		H	H	CH3-	H
A1569	CH3-		H	H	CH3-	H
A1570	CH3-		H	H	CH3-	H
A1571	CH3-		H	H	CH3-	H
A1572	CH3-		H	H	CH3-	H
A1573	CH3-		H	H	CH3-	H
A1574	CH3-		H	H	CH3-	H
A1575	CH3-		H	H	CH3-	H
A1576	CH3-		H	H	CH3-	H
A1577	CH3-		H	H	CH3-	H
A1578	CH3-		H	H	CH3-	H
A1579	CH3-		H	H	CH3-	H
A1580	CH3-		H	H	CH3-	H
A1581	CH3-		H	H	CH3-	H
A1582	CH3-		H	H	CH3-	H
A1583	CH3-		H	H	CH3-	H
A1584	CH3-		H	H	CH3-	H
A1585	CH3-		H	H	CH3-	H
A1586	CH3-		H	H	CH3-	H




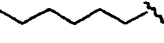
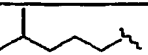

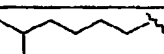

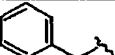
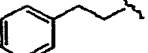
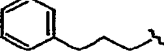



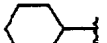
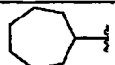





No.	R1	R2	R3	R4	R5	R6
A1587	CH3-		H	H	CH3-	H
A1588	CH3-		H	H	CH3-	H
A1589	CH3-		H	H	CH3-	H
A1590	CH3-		H	H	CH3-	H
A1591	CH3-		H	H	CH3-	H
A1592	CH3-		H	H	CH3-	H
A1593	CH3-	CH3-	H	H	CH3-	CH3-
A1594	CH3-	CH3CH2-	H	H	CH3-	CH3-
A1595	CH3-		H	H	CH3-	CH3-
A1596	CH3-		H	H	CH3-	CH3-
A1597	CH3-		H	H	CH3-	CH3-
A1598	CH3-		H	H	CH3-	CH3-
A1599	CH3-		H	H	CH3-	CH3-
A1600	CH3-		H	H	CH3-	CH3-
A1601	CH3-		H	H	CH3-	CH3-
A1602	CH3-		H	H	CH3-	CH3-
A1603	CH3-		H	H	CH3-	CH3-
A1604	CH3-		H	H	CH3-	CH3-
A1605	CH3-		H	H	CH3-	CH3-
A1606	CH3-		H	H	CH3-	CH3-
A1607	CH3-		H	H	CH3-	CH3-
A1608	CH3-		H	H	CH3-	CH3-




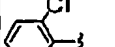
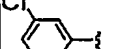
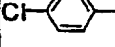
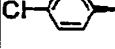
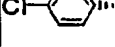
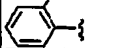
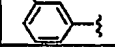

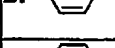
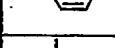
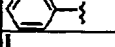

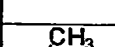
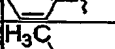
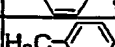
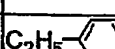
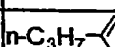
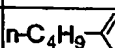

No.	R1	R2	R3	R4	R5	R6
A1609	CH3-	n-C8H17-	H	H	CH3-	CH3-
A1610	CH3-		H	H	CH3-	CH3-
A1611	CH3-		H	H	CH3-	CH3-
A1612	CH3-		H	H	CH3-	CH3-
A1613	CH3-		H	H	CH3-	CH3-
A1614	CH3-		H	H	CH3-	CH3-
A1615	CH3-		H	H	CH3-	CH3-
A1616	CH3-		H	H	CH3-	CH3-
A1617	CH3-		H	H	CH3-	CH3-
A1618	CH3-		H	H	CH3-	CH3-
A1619	CH3-		H	H	CH3-	CH3-
A1620	CH3-		H	H	CH3-	CH3-
A1621	CH3-		H	H	CH3-	CH3-
A1622	CH3-		H	H	CH3-	CH3-
A1623	CH3-		H	H	CH3-	CH3-
A1624	CH3-		H	H	CH3-	CH3-
A1625	CH3-		H	H	CH3-	CH3-
A1626	CH3-		H	H	CH3-	CH3-
A1627	CH3-		H	H	CH3-	CH3-
A1628	CH3-		H	H	CH3-	CH3-
A1629	CH3-		H	H	CH3-	CH3-
A1630	CH3-		H	H	CH3-	CH3-

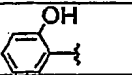
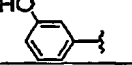
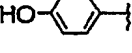
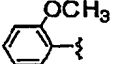
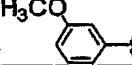
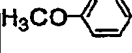
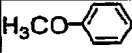
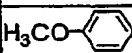
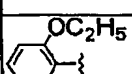
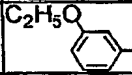
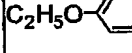
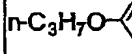
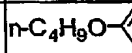
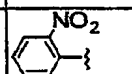
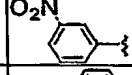
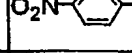
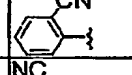
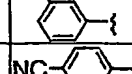
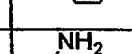
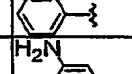
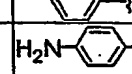
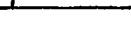
No.	R1	R2	R3	R4	R5	R6
A1631	CH ₃ -		H	H	CH ₃ -	CH ₃ -
A1632	CH ₃ -		H	H	CH ₃ -	CH ₃ -
A1633	CH ₃ -		H	H	CH ₃ -	CH ₃ -
A1634	CH ₃ -		H	H	CH ₃ -	CH ₃ -
A1635	CH ₃ -		H	H	CH ₃ -	CH ₃ -
A1636	CH ₃ -		H	H	CH ₃ -	CH ₃ -
A1637	CH ₃ -		H	H	CH ₃ -	CH ₃ -
A1638	CH ₃ -		H	H	CH ₃ -	CH ₃ -
A1639	CH ₃ -		H	H	CH ₃ -	CH ₃ -
A1640	CH ₃ -		H	H	CH ₃ -	CH ₃ -
A1641	CH ₃ -		H	H	CH ₃ -	CH ₃ -
A1642	CH ₃ -		H	H	CH ₃ -	CH ₃ -
A1643	CH ₃ -		H	H	CH ₃ -	CH ₃ -
A1644	CH ₃ -		H	H	CH ₃ -	CH ₃ -
A1645	CH ₃ -		H	H	CH ₃ -	CH ₃ -
A1646	CH ₃ -		H	H	CH ₃ -	CH ₃ -
A1647	CH ₃ -		H	H	CH ₃ -	CH ₃ -
A1648	CH ₃ -		H	H	CH ₃ -	CH ₃ -
A1649	CH ₃ -		H	H	CH ₃ -	CH ₃ -
A1650	CH ₃ -		H	H	CH ₃ -	CH ₃ -
A1651	CH ₃ -		H	H	CH ₃ -	CH ₃ -
A1652	CH ₃ -		H	H	CH ₃ -	CH ₃ -

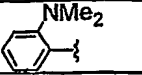
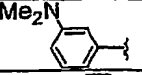
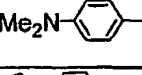
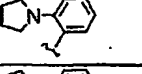
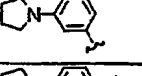
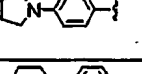
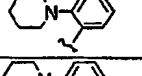
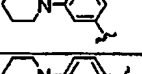
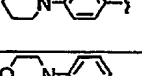
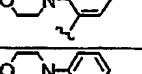
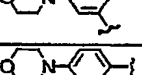
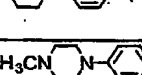
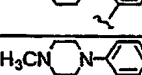
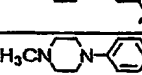
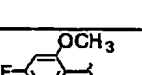
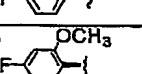
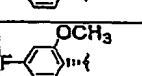
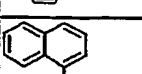
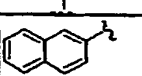
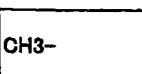
No.	R1	R2	R3	R4	R5	R6
A1653	CH ₃ -		H	H	CH ₃ -	CH ₃ -
A1654	CH ₃ -		H	H	CH ₃ -	CH ₃ -
A1655	CH ₃ -		H	H	CH ₃ -	CH ₃ -
A1656	CH ₃ -		H	H	CH ₃ -	CH ₃ -
A1657	CH ₃ -		H	H	CH ₃ -	CH ₃ -
A1658	CH ₃ -		H	H	CH ₃ -	CH ₃ -
A1659	CH ₃ -		H	H	CH ₃ -	CH ₃ -
A1660	CH ₃ -		H	H	CH ₃ -	CH ₃ -
A1661	CH ₃ -		H	H	CH ₃ -	CH ₃ -
A1662	CH ₃ -		H	H	CH ₃ -	CH ₃ -
A1663	CH ₃ -		H	H	CH ₃ -	CH ₃ -
A1664	CH ₃ -		H	H	CH ₃ -	CH ₃ -
A1665	CH ₃ -		H	H	CH ₃ -	CH ₃ -
A1666	CH ₃ -		H	H	CH ₃ -	CH ₃ -
A1667	CH ₃ -		H	H	CH ₃ -	CH ₃ -
A1668	CH ₃ -		H	H	CH ₃ -	CH ₃ -
A1669	CH ₃ -		H	H	CH ₃ -	CH ₃ -
A1670	CH ₃ -		H	H	CH ₃ -	CH ₃ -
A1671	CH ₃ -		H	H	CH ₃ -	CH ₃ -
A1672	CH ₃ -		H	H	CH ₃ -	CH ₃ -
A1673	CH ₃ -		H	H	CH ₃ -	CH ₃ -
A1674	CH ₃ -		H	H	CH ₃ -	CH ₃ -








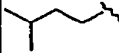



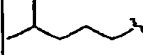

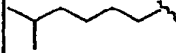
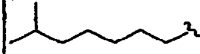
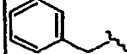
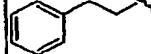
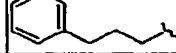



No.	R1	R2	R3	R4	R5	R6
A1675	CH3-		H	H	CH3-	CH3-
A1676	CH3-		H	H	CH3-	CH3-
A1677	CH3-		H	H	CH3-	CH3-
A1678	CH3-		H	H	CH3-	CH3-
A1679	CH3-		H	H	CH3-	CH3-
A1680	CH3-		H	H	CH3-	CH3-
A1681	CH3-		H	H	CH3-	CH3-
A1682	CH3-		H	H	CH3-	CH3-
A1683	CH3-		H	H	CH3-	CH3-
A1684	CH3-		H	H	CH3-	CH3-
A1685	CH3-		H	H	CH3-	CH3-
A1686	CH3-		H	H	CH3-	CH3-
A1687	CH3-		H	H	CH3-	CH3-
A1688	CH3-	CH3-	H	CH3-	CH3-	CH3-
A1689	CH3-	CH3CH2-	H	CH3-	CH3-	CH3-
A1690	CH3-		H	CH3-	CH3-	CH3-
A1691	CH3-		H	CH3-	CH3-	CH3-
A1692	CH3-		H	CH3-	CH3-	CH3-
A1693	CH3-		H	CH3-	CH3-	CH3-
A1694	CH3-		H	CH3-	CH3-	CH3-
A1695	CH3-		H	CH3-	CH3-	CH3-
A1696	CH3-		H	CH3-	CH3-	CH3-

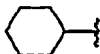
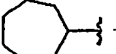




















No.	R1	R2	R3	R4	R5	R6
A1697	CH3-		H	CH3-	CH3-	CH3-
A1698	CH3-		H	CH3-	CH3-	CH3-
A1699	CH3-		H	CH3-	CH3-	CH3-
A1700	CH3-		H	CH3-	CH3-	CH3-
A1701	CH3-		H	CH3-	CH3-	CH3-
A1702	CH3-		H	CH3-	CH3-	CH3-
A1703	CH3-		H	CH3-	CH3-	CH3-
A1704	CH3-	n-C8H17-	H	CH3-	CH3-	CH3-
A1705	CH3-		H	CH3-	CH3-	CH3-
A1706	CH3-		H	CH3-	CH3-	CH3-
A1707	CH3-		H	CH3-	CH3-	CH3-
A1708	CH3-		H	CH3-	CH3-	CH3-
A1709	CH3-		H	CH3-	CH3-	CH3-
A1710	CH3-		H	CH3-	CH3-	CH3-
A1711	CH3-		H	CH3-	CH3-	CH3-
A1712	CH3-		H	CH3-	CH3-	CH3-
A1713	CH3-		H	CH3-	CH3-	CH3-
A1714	CH3-		H	CH3-	CH3-	CH3-
A1715	CH3-		H	CH3-	CH3-	CH3-
A1716	CH3-		H	CH3-	CH3-	CH3-
A1717	CH3-		H	CH3-	CH3-	CH3-
A1718	CH3-		H	CH3-	CH3-	CH3-

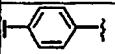
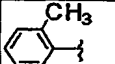
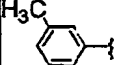
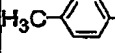
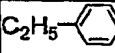
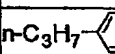
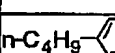
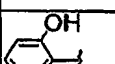
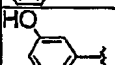
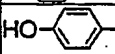
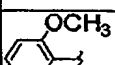
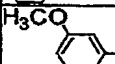
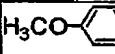
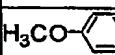
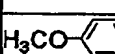
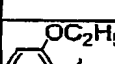
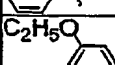
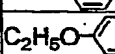
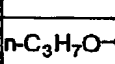
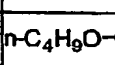
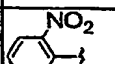
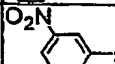
No.	R1	R2	R3	R4	R5	R6
A1719	CH ₃ -		H	CH ₃ -	CH ₃ -	CH ₃ -
A1720	CH ₃ -		H	CH ₃ -	CH ₃ -	CH ₃ -
A1721	CH ₃ -		H	CH ₃ -	CH ₃ -	CH ₃ -
A1722	CH ₃ -		H	CH ₃ -	CH ₃ -	CH ₃ -
A1723	CH ₃ -		H	CH ₃ -	CH ₃ -	CH ₃ -
A1724	CH ₃ -		H	CH ₃ -	CH ₃ -	CH ₃ -
A1725	CH ₃ -		H	CH ₃ -	CH ₃ -	CH ₃ -
A1726	CH ₃ -		H	CH ₃ -	CH ₃ -	CH ₃ -
A1727	CH ₃ -		H	CH ₃ -	CH ₃ -	CH ₃ -
A1728	CH ₃ -		H	CH ₃ -	CH ₃ -	CH ₃ -
A1729	CH ₃ -		H	CH ₃ -	CH ₃ -	CH ₃ -
A1730	CH ₃ -		H	CH ₃ -	CH ₃ -	CH ₃ -
A1731	CH ₃ -		H	CH ₃ -	CH ₃ -	CH ₃ -
A1732	CH ₃ -		H	CH ₃ -	CH ₃ -	CH ₃ -
A1733	CH ₃ -		H	CH ₃ -	CH ₃ -	CH ₃ -
A1734	CH ₃ -		H	CH ₃ -	CH ₃ -	CH ₃ -
A1735	CH ₃ -		H	CH ₃ -	CH ₃ -	CH ₃ -
A1736	CH ₃ -		H	CH ₃ -	CH ₃ -	CH ₃ -
A1737	CH ₃ -		H	CH ₃ -	CH ₃ -	CH ₃ -
A1738	CH ₃ -		H	CH ₃ -	CH ₃ -	CH ₃ -
A1739	CH ₃ -		H	CH ₃ -	CH ₃ -	CH ₃ -
A1740	CH ₃ -		H	CH ₃ -	CH ₃ -	CH ₃ -

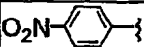

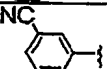
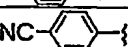

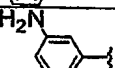
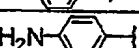
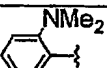
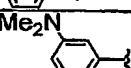
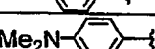

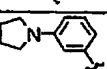
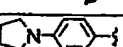
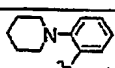
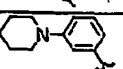
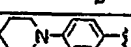
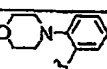
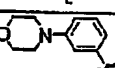
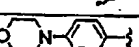
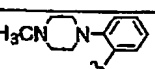
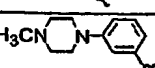
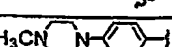
No.	R1	R2	R3	R4	R5	R6
A1741	CH3-		H	CH3-	CH3-	CH3-
A1742	CH3-		H	CH3-	CH3-	CH3-
A1743	CH3-		H	CH3-	CH3-	CH3-
A1744	CH3-		H	CH3-	CH3-	CH3-
A1745	CH3-		H	CH3-	CH3-	CH3-
A1746	CH3-		H	CH3-	CH3-	CH3-
A1747	CH3-		H	CH3-	CH3-	CH3-
A1748	CH3-		H	CH3-	CH3-	CH3-
A1749	CH3-		H	CH3-	CH3-	CH3-
A1750	CH3-		H	CH3-	CH3-	CH3-
A1751	CH3-		H	CH3-	CH3-	CH3-
A1752	CH3-		H	CH3-	CH3-	CH3-
A1753	CH3-		H	CH3-	CH3-	CH3-
A1754	CH3-		H	CH3-	CH3-	CH3-
A1755	CH3-		H	CH3-	CH3-	CH3-
A1756	CH3-		H	CH3-	CH3-	CH3-
A1757	CH3-		H	CH3-	CH3-	CH3-
A1758	CH3-		H	CH3-	CH3-	CH3-
A1759	CH3-		H	CH3-	CH3-	CH3-
A1760	CH3-		H	CH3-	CH3-	CH3-
A1761	CH3-		H	CH3-	CH3-	CH3-
A1762	CH3-		H	CH3-	CH3-	CH3-

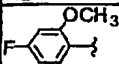
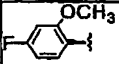
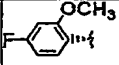
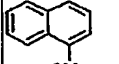
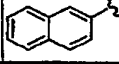



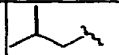
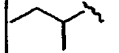





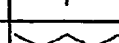
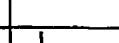


No.	R1	R2	R3	R4	R5	R6
A1763	CH3-		H	CH3-	CH3-	CH3-
A1764	CH3-		H	CH3-	CH3-	CH3-
A1765	CH3-		H	CH3-	CH3-	CH3-
A1766	CH3-		H	CH3-	CH3-	CH3-
A1767	CH3-		H	CH3-	CH3-	CH3-
A1768	CH3-		H	CH3-	CH3-	CH3-
A1769	CH3-		H	CH3-	CH3-	CH3-
A1770	CH3-		H	CH3-	CH3-	CH3-
A1771	CH3-		H	CH3-	CH3-	CH3-
A1772	CH3-		H	CH3-	CH3-	CH3-
A1773	CH3-		H	CH3-	CH3-	CH3-
A1774	CH3-		H	CH3-	CH3-	CH3-
A1775	CH3-		H	CH3-	CH3-	CH3-
A1776	CH3-		H	CH3-	CH3-	CH3-
A1777	CH3-		H	CH3-	CH3-	CH3-
A1778	CH3-		H	CH3-	CH3-	CH3-
A1779	CH3-		H	CH3-	CH3-	CH3-
A1780	CH3-		H	CH3-	CH3-	CH3-
A1781	CH3-		H	CH3-	CH3-	CH3-
A1782	CH3-		H	CH3-	CH3-	CH3-
A1783	CH3CH2-	CH3-	H	H	H	H
A1784	CH3CH2-	CH3CH2-	H	H	H	H

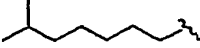
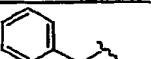
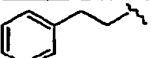
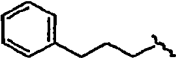


















No.	R1	R2	R3	R4	R5	R6
A1785	CH ₃ CH ₂ -		H	H	H	H
A1786	CH ₃ CH ₂ -		H	H	H	H
A1787	CH ₃ CH ₂ -		H	H	H	H
A1788	CH ₃ CH ₂ -		H	H	H	H
A1789	CH ₃ CH ₂ -		H	H	H	H
A1790	CH ₃ CH ₂ -		H	H	H	H
A1791	CH ₃ CH ₂ -		H	H	H	H
A1792	CH ₃ CH ₂ -		H	H	H	H
A1793	CH ₃ CH ₂ -		H	H	H	H
A1794	CH ₃ CH ₂ -		H	H	H	H
A1795	CH ₃ CH ₂ -		H	H	H	H
A1796	CH ₃ CH ₂ -		H	H	H	H
A1797	CH ₃ CH ₂ -		H	H	H	H
A1798	CH ₃ CH ₂ -		H	H	H	H
A1799	CH ₃ CH ₂ -	n-C ₈ H ₁₇ -	H	H	H	H
A1800	CH ₃ CH ₂ -		H	H	H	H
A1801	CH ₃ CH ₂ -		H	H	H	H
A1802	CH ₃ CH ₂ -		H	H	H	H
A1803	CH ₃ CH ₂ -		H	H	H	H
A1804	CH ₃ CH ₂ -		H	H	H	H
A1805	CH ₃ CH ₂ -		H	H	H	H
A1806	CH ₃ CH ₂ -		H	H	H	H

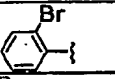
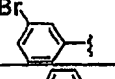
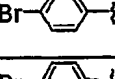
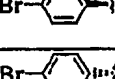
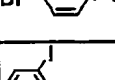
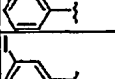
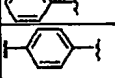
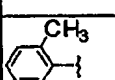
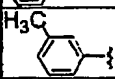
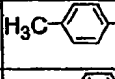
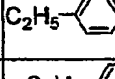
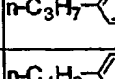
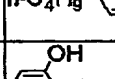
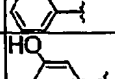
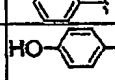
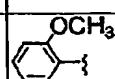
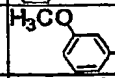
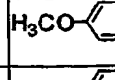
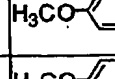
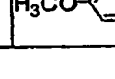


No.	R1	R2	R3	R4	R5	R6
A1807	CH ₃ CH ₂ -		H	H	H	H
A1808	CH ₃ CH ₂ -		H	H	H	H
A1809	CH ₃ CH ₂ -		H	H	H	H
A1810	CH ₃ CH ₂ -		H	H	H	H
A1811	CH ₃ CH ₂ -		H	H	H	H
A1812	CH ₃ CH ₂ -		H	H	H	H
A1813	CH ₃ CH ₂ -		H	H	H	H
A1814	CH ₃ CH ₂ -		H	H	H	H
A1815	CH ₃ CH ₂ -		H	H	H	H
A1816	CH ₃ CH ₂ -		H	H	H	H
A1817	CH ₃ CH ₂ -		H	H	H	H
A1818	CH ₃ CH ₂ -		H	H	H	H
A1819	CH ₃ CH ₂ -		H	H	H	H
A1820	CH ₃ CH ₂ -		H	H	H	H
A1821	CH ₃ CH ₂ -		H	H	H	H
A1822	CH ₃ CH ₂ -		H	H	H	H
A1823	CH ₃ CH ₂ -		H	H	H	H
A1824	CH ₃ CH ₂ -		H	H	H	H
A1825	CH ₃ CH ₂ -		H	H	H	H
A1826	CH ₃ CH ₂ -		H	H	H	H
A1827	CH ₃ CH ₂ -		H	H	H	H
A1828	CH ₃ CH ₂ -		H	H	H	H

No.	R1	R2	R3	R4	R5	R6
A1829	CH ₃ CH ₂ -		H	H	H	H
A1830	CH ₃ CH ₂ -		H	H	H	H
A1831	CH ₃ CH ₂ -		H	H	H	H
A1832	CH ₃ CH ₂ -		H	H	H	H
A1833	CH ₃ CH ₂ -		H	H	H	H
A1834	CH ₃ CH ₂ -		H	H	H	H
A1835	CH ₃ CH ₂ -		H	H	H	H
A1836	CH ₃ CH ₂ -		H	H	H	H
A1837	CH ₃ CH ₂ -		H	H	H	H
A1838	CH ₃ CH ₂ -		H	H	H	H
A1839	CH ₃ CH ₂ -		H	H	H	H
A1840	CH ₃ CH ₂ -		H	H	H	H
A1841	CH ₃ CH ₂ -		H	H	H	H
A1842	CH ₃ CH ₂ -		H	H	H	H
A1843	CH ₃ CH ₂ -		H	H	H	H
A1844	CH ₃ CH ₂ -		H	H	H	H
A1845	CH ₃ CH ₂ -		H	H	H	H
A1846	CH ₃ CH ₂ -		H	H	H	H
A1847	CH ₃ CH ₂ -		H	H	H	H
A1848	CH ₃ CH ₂ -		H	H	H	H
A1849	CH ₃ CH ₂ -		H	H	H	H
A1850	CH ₃ CH ₂ -		H	H	H	H

No.	R1	R2	R3	R4	R5	R6
A1851	CH ₃ CH ₂ -		H	H	H	H
A1852	CH ₃ CH ₂ -		H	H	H	H
A1853	CH ₃ CH ₂ -		H	H	H	H
A1854	CH ₃ CH ₂ -		H	H	H	H
A1855	CH ₃ CH ₂ -		H	H	H	H
A1856	CH ₃ CH ₂ -		H	H	H	H
A1857	CH ₃ CH ₂ -		H	H	H	H
A1858	CH ₃ CH ₂ -		H	H	H	H
A1859	CH ₃ CH ₂ -		H	H	H	H
A1860	CH ₃ CH ₂ -		H	H	H	H
A1861	CH ₃ CH ₂ -		H	H	H	H
A1862	CH ₃ CH ₂ -		H	H	H	H
A1863	CH ₃ CH ₂ -		H	H	H	H
A1864	CH ₃ CH ₂ -		H	H	H	H
A1865	CH ₃ CH ₂ -		H	H	H	H
A1866	CH ₃ CH ₂ -		H	H	H	H
A1867	CH ₃ CH ₂ -		H	H	H	H
A1868	CH ₃ CH ₂ -		H	H	H	H
A1869	CH ₃ CH ₂ -		H	H	H	H
A1870	CH ₃ CH ₂ -		H	H	H	H
A1871	CH ₃ CH ₂ -		H	H	H	H
A1872	CH ₃ CH ₂ -		H	H	H	H

No.	R1	R2	R3	R4	R5	R6
A1873	CH ₃ CH ₂ -		H	H	H	H
A1874	CH ₃ CH ₂ -		H	H	H	H
A1875	CH ₃ CH ₂ -		H	H	H	H
A1876	CH ₃ CH ₂ -		H	H	H	H
A1877	CH ₃ CH ₂ -		H	H	H	H
A1878	CH ₃ CH ₂ -	CH ₃ -	H	CH ₃ -	H	H
A1879	CH ₃ CH ₂ -	CH ₃ CH ₂ -	H	CH ₃ -	H	H
A1880	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1881	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1882	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1883	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1884	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1885	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1886	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1887	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1888	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1889	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1890	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1891	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1892	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1893	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1894	CH ₃ CH ₂ -	n-C ₈ H ₁₇ -	H	CH ₃ -	H	H

No.	R1	R2	R3	R4	R5	R6
A1895	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1896	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1897	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1898	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1899	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1900	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1901	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1902	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1903	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1904	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1905	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1906	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1907	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1908	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1909	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1910	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1911	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1912	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1913	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1914	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1915	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1916	CH ₃ CH ₂ -		H	CH ₃ -	H	H

No.	R1	R2	R3	R4	R5	R6
A1917	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1918	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1919	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1920	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1921	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1922	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1923	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1924	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1925	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1926	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1927	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1928	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1929	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1930	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1931	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1932	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1933	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1934	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1935	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1936	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1937	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1938	CH ₃ CH ₂ -		H	CH ₃ -	H	H

No.	R1	R2	R3	R4	R5	R6
A1939	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1940	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1941	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1942	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1943	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1944	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1945	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1946	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1947	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1948	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1949	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1950	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1951	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1952	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1953	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1954	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1955	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1956	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1957	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1958	CH ₃ CH ₂ -		H	CH ₃ -	H	H
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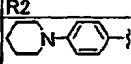
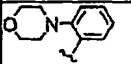
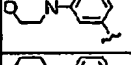
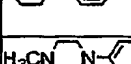
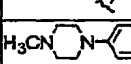
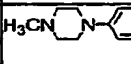
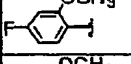
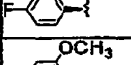
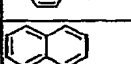
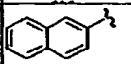


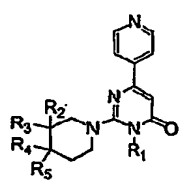



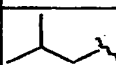




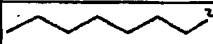

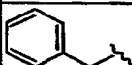
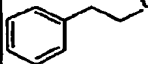





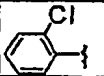
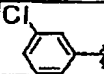
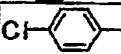
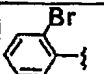
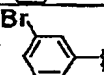
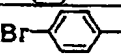
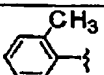
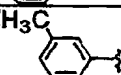
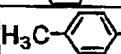
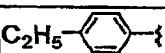
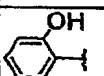
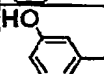
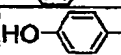
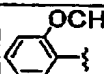
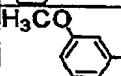
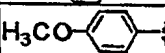
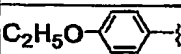
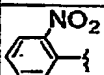
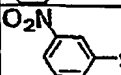
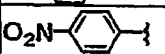



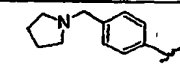

















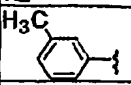
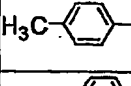
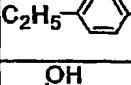
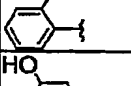
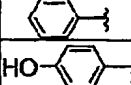
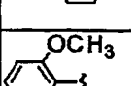
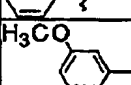
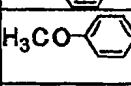
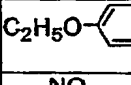
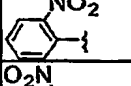
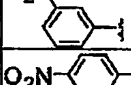
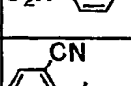
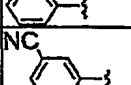
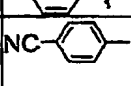
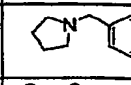
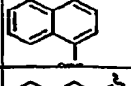
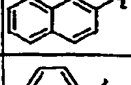
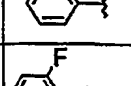



No.	R1	R2	R3	R4	R5	R6
A1961	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1962	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1963	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1964	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1965	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1966	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1967	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1968	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1969	CH ₃ CH ₂ -		H	CH ₃ -	H	H
A1970	CH ₃ CH ₂ -		H	CH ₃ -	H	H
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A1972	CH ₃ CH ₂ -		H	CH ₃ -	H	H

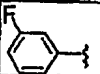
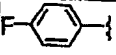
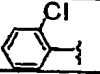
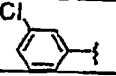

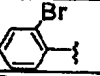
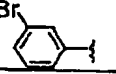
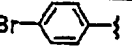
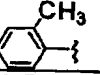
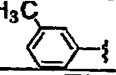
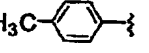
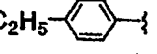
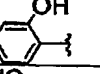

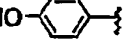
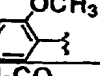
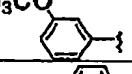
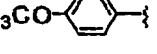
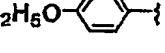
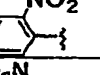
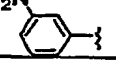
Table-2

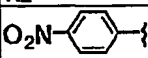

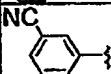
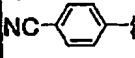
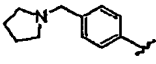

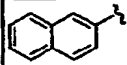



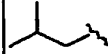






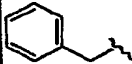
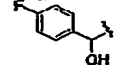
					
No	R1	R2	R3	R4	R5
B1	CH3-	CH3-	H	H	H
B2	CH3-	CH3CH2-	H	H	H
B3	CH3-		H	H	H
B4	CH3-		H	H	H
B5	CH3-		H	H	H
B6	CH3-		H	H	H
B7	CH3-		H	H	H
B8	CH3-		H	H	H
B9	CH3-		H	H	H
B10	CH3-		H	H	H
B11	CH3-		H	H	H
B12	CH3-		H	H	H
B13	CH3-		H	H	H
B14	CH3-		H	H	H
B15	CH3-		H	H	H
B16	CH3-		H	H	H
B17	CH3-		H	H	H
B18	CH3-		H	H	H

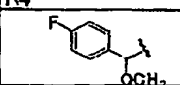
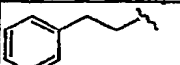

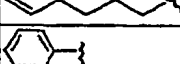
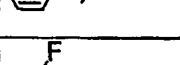
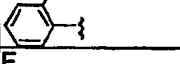
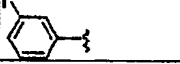
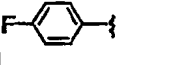
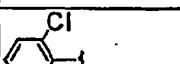
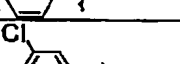
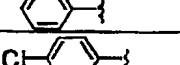
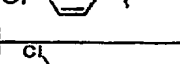
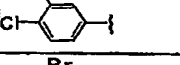
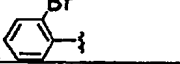
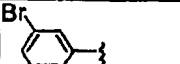
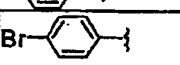
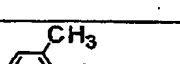
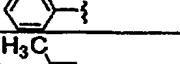

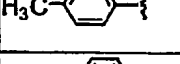
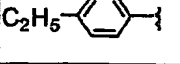
No	R1	R2	R3	R4	R5
B19	CH3-		H	H	H
B20	CH3-		H	H	H
B21	CH3-		H	H	H
B22	CH3-		H	H	H
B23	CH3-		H	H	H
B24	CH3-		H	H	H
B25	CH3-		H	H	H
B26	CH3-		H	H	H
B27	CH3-		H	H	H
B28	CH3-		H	H	H
B29	CH3-		H	H	H
B30	CH3-		H	H	H
B31	CH3-		H	H	H
B32	CH3-		H	H	H
B33	CH3-		H	H	H
B34	CH3-		H	H	H
B35	CH3-		H	H	H
B36	CH3-		H	H	H
B37	CH3-		H	H	H
B38	CH3-		H	H	H
B39	CH3-		H	H	H

No	R1	R2	R3	R4	R5
B40	CH3-		H	H	H
B41	CH3-		H	H	H
B42	CH3-		H	H	H
B43	CH3-		H	H	H
B44	CH3-		H	H	H
B45	CH3-		H	H	H
B46	CH3-		H	H	H
B47	CH3-		H	H	H
B48	CH3-		H	H	H
B49	CH3-		H	H	H
B50	CH3-		OH	H	H
B51	CH3-		OH	H	H
B52	CH3-		OH	H	H
B53	CH3-		OH	H	H
B54	CH3-		OH	H	H
B55	CH3-		OH	H	H
B56	CH3-		OH	H	H
B57	CH3-		OH	H	H
B58	CH3-		OH	H	H
B59	CH3-		OH	H	H
B60	CH3-		OH	H	H

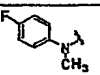
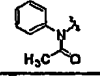
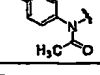


















No	R1	R2	R3	R4	R5
B61	CH ₃ -		OH	H	H
B62	CH ₃ -		OH	H	H
B63	CH ₃ -		OH	H	H
B64	CH ₃ -		OH	H	H
B65	CH ₃ -		OH	H	H
B66	CH ₃ -		OH	H	H
B67	CH ₃ -		OH	H	H
B68	CH ₃ -		OH	H	H
B69	CH ₃ -		OH	H	H
B70	CH ₃ -		OH	H	H
B71	CH ₃ -		OH	H	H
B72	CH ₃ -		OH	H	H
B73	CH ₃ -		OH	H	H
B74	CH ₃ -		OH	H	H
B75	CH ₃ -		OH	H	H
B76	CH ₃ -		OH	H	H
B77	CH ₃ -		OH	H	H
B78	CH ₃ -		OH	H	H
B79	CH ₃ -		OH	H	H
B80	CH ₃ -		CN	H	H
B81	CH ₃ -		CN	H	H

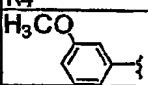
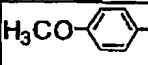
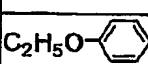
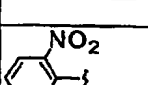
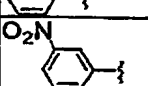
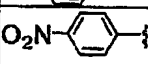
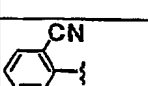
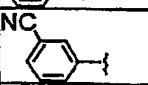
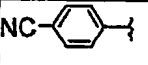
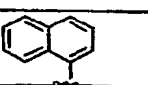
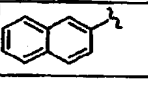
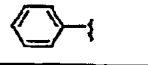
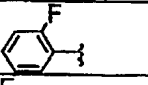
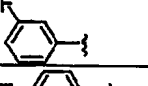
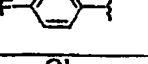
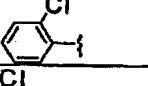
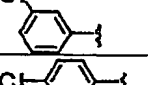
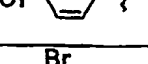
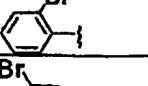
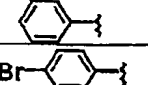

No	R1	R2	R3	R4	R5
B82	CH ₃ -		CN	H	H
B83	CH ₃ -		CN	H	H
B84	CH ₃ -		CN	H	H
B85	CH ₃ -		CN	H	H
B86	CH ₃ -		CN	H	H
B87	CH ₃ -		CN	H	H
B88	CH ₃ -		CN	H	H
B89	CH ₃ -		CN	H	H
B90	CH ₃ -		CN	H	H
B91	CH ₃ -		CN	H	H
B92	CH ₃ -		CN	H	H
B93	CH ₃ -		CN	H	H
B94	CH ₃ -		CN	H	H
B95	CH ₃ -		CN	H	H
B96	CH ₃ -		CN	H	H
B97	CH ₃ -		CN	H	H
B98	CH ₃ -		CN	H	H
B99	CH ₃ -		CN	H	H
B100	CH ₃ -		CN	H	H
B101	CH ₃ -		CN	H	H
B102	CH ₃ -		CN	H	H

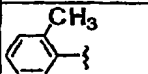
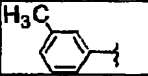
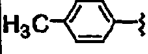
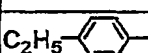
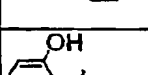
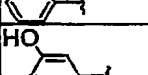
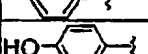
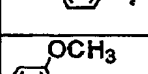
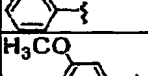

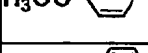
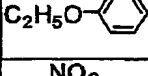
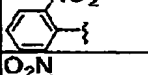
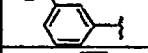
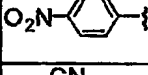
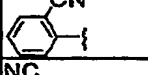
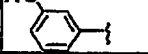
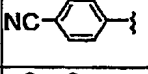
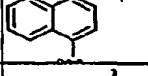
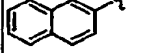

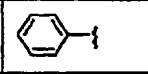

No	R1	R2	R3	R4	R5
B103	CH ₃ -		CN	H	H
B104	CH ₃ -		CN	H	H
B105	CH ₃ -		CN	H	H
B106	CH ₃ -		CN	H	H
B107	CH ₃ -		CN	H	H
B108	CH ₃ -		CN	H	H
B109	CH ₃ -		CN	H	H
B110	CH ₃ -	H	H	CH ₃ -	H
B111	CH ₃ -	H	H	CH ₃ CH ₂ -	H
B112	CH ₃ -	H	H		H
B113	CH ₃ -	H	H		H
B114	CH ₃ -	H	H		H
B115	CH ₃ -	H	H		H
B116	CH ₃ -	H	H		H
B117	CH ₃ -	H	H		H
B118	CH ₃ -	H	H		H
B119	CH ₃ -	H	H		H
B120	CH ₃ -	H	H		H
B121	CH ₃ -	H	H		H
B122	CH ₃ -	H	H		H
B123	CH ₃ -	H	H		H

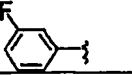

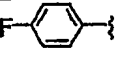

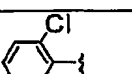

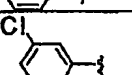

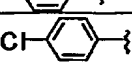

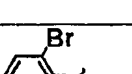

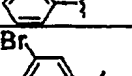

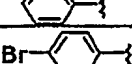

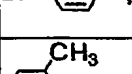

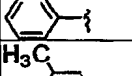

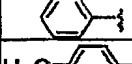

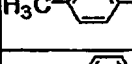

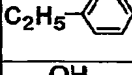

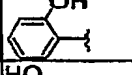

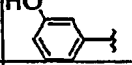

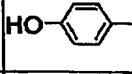

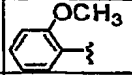

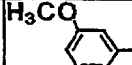

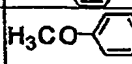

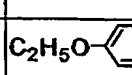

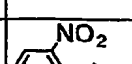

No	R1	R2	R3	R4	R5
B124	CH ₃ -	H	H		H
B125	CH ₃ -	H	H		H
B126	CH ₃ -	H	H		H
B127	CH ₃ -	H	H		H
B128	CH ₃ -	H	H		H
B129	CH ₃ -	H	H		H
B130	CH ₃ -	H	H		H
B131	CH ₃ -	H	H		H
B132	CH ₃ -	H	H		H
B133	CH ₃ -	H	H		H
B134	CH ₃ -	H	H		H
B135	CH ₃ -	H	H		H
B136	CH ₃ -	H	H		H
B137	CH ₃ -	H	H		H
B138	CH ₃ -	H	H		H
B139	CH ₃ -	H	H		H
B140	CH ₃ -	H	H		H
B141	CH ₃ -	H	H		H
B142	CH ₃ -	H	H		H
B143	CH ₃ -	H	H		H
B144	CH ₃ -	H	H		H

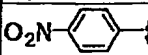



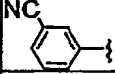

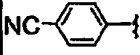



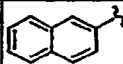

No	R1	R2	R3	R4	R5
B145	CH ₃ -	H	H		H
B146	CH ₃ -	H	H		H
B147	CH ₃ -	H	H		H
B148	CH ₃ -	H	H		H
B149	CH ₃ -	H	H		H
B150	CH ₃ -	H	H		H
B151	CH ₃ -	H	H		H
B152	CH ₃ -	H	H		H
B153	CH ₃ -	H	H		H
B154	CH ₃ -	H	H		H
B155	CH ₃ -	H	H		H
B156	CH ₃ -	H	H		H
B157	CH ₃ -	H	H		H
B158	CH ₃ -	H	H		H
B159	CH ₃ -	H	H		H
B160	CH ₃ -	H	H		H
B161	CH ₃ -	H	H		H
B162	CH ₃ -	H	H		H
B163	CH ₃ -	H	H		H
B164	CH ₃ -	H	H		H
B165	CH ₃ -	H	H		H

No	R1	R2	R3	R4	R5
B166	CH ₃ -	H	H		H
B167	CH ₃ -	H	H		H
B168	CH ₃ -	H	H		H
B169	CH ₃ -	H	H		OH
B170	CH ₃ -	H	H		OH
B171	CH ₃ -	H	H		OH
B172	CH ₃ -	H	H		OH
B173	CH ₃ -	H	H		OH
B174	CH ₃ -	H	H		OH
B175	CH ₃ -	H	H		OH
B176	CH ₃ -	H	H		OH
B177	CH ₃ -	H	H		OH
B178	CH ₃ -	H	H		OH
B179	CH ₃ -	H	H		OH
B180	CH ₃ -	H	H		OH
B181	CH ₃ -	H	H		OH
B182	CH ₃ -	H	H		OH
B183	CH ₃ -	H	H		OH
B184	CH ₃ -	H	H		OH
B185	CH ₃ -	H	H		OH
B186	CH ₃ -	H	H		OH

No	R1	R2	R3	R4	R5
B187	CH ₃ -	H	H		OH
B188	CH ₃ -	H	H		OH
B189	CH ₃ -	H	H		OH
B190	CH ₃ -	H	H		OH
B191	CH ₃ -	H	H		OH
B192	CH ₃ -	H	H		OH
B193	CH ₃ -	H	H		OH
B194	CH ₃ -	H	H		OH
B195	CH ₃ -	H	H		OH
B196	CH ₃ -	H	H		OH
B197	CH ₃ -	H	H		OH
B198	CH ₃ -	H	H		CN
B199	CH ₃ -	H	H		CN
B200	CH ₃ -	H	H		CN
B201	CH ₃ -	H	H		CN
B202	CH ₃ -	H	H		CN
B203	CH ₃ -	H	H		CN
B204	CH ₃ -	H	H		CN
B205	CH ₃ -	H	H		CN
B206	CH ₃ -	H	H		CN
B207	CH ₃ -	H	H		CN

No	R1	R2	R3	R4	R5
B208	CH ₃ -	H	H		CN
B209	CH ₃ -	H	H		CN
B210	CH ₃ -	H	H		CN
B211	CH ₃ -	H	H		CN
B212	CH ₃ -	H	H		CN
B213	CH ₃ -	H	H		CN
B214	CH ₃ -	H	H		CN
B215	CH ₃ -	H	H		CN
B216	CH ₃ -	H	H		CN
B217	CH ₃ -	H	H		CN
B218	CH ₃ -	H	H		CN
B219	CH ₃ -	H	H		CN
B220	CH ₃ -	H	H		CN
B221	CH ₃ -	H	H		CN
B222	CH ₃ -	H	H		CN
B223	CH ₃ -	H	H		CN
B224	CH ₃ -	H	H		CN
B225	CH ₃ -	H	H		CN
B226	CH ₃ -	H	H		CN
B227	CH ₃ -	H	H		
B228	CH ₃ -	H	H		

No	R1	R2	R3	R4	R5
B229	CH ₃ -	H	H		
B230	CH ₃ -	H	H		
B231	CH ₃ -	H	H		
B232	CH ₃ -	H	H		
B233	CH ₃ -	H	H		
B234	CH ₃ -	H	H		
B235	CH ₃ -	H	H		
B236	CH ₃ -	H	H		
B237	CH ₃ -	H	H		
B238	CH ₃ -	H	H		
B239	CH ₃ -	H	H		
B240	CH ₃ -	H	H		
B241	CH ₃ -	H	H		
B242	CH ₃ -	H	H		
B243	CH ₃ -	H	H		
B244	CH ₃ -	H	H		
B245	CH ₃ -	H	H		
B246	CH ₃ -	H	H		
B247	CH ₃ -	H	H		
B248	CH ₃ -	H	H		
B249	CH ₃ -	H	H		

No	R1	R2	R3	R4	R5
B250	CH ₃ -	H	H		
B251	CH ₃ -	H	H		
B252	CH ₃ -	H	H		
B253	CH ₃ -	H	H		
B254	CH ₃ -	H	H		
B255	CH ₃ -	H	H		

Particularly preferred compounds of the present invention represented by formula (I) include:

2-(3-Phenylpiperazin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-pyrimidin-4-one;
2-(3-(4-Fluorophenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-pyrimidin-4-one;
2-(3-(3-Fluorophenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-pyrimidin-4-one;
2-(3-(2-Fluorophenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-pyrimidin-4-one;
2-(3-(4-Chlorophenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-pyrimidin-4-one;
(*S*)-2-(3-(4-Chlorophenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-pyrimidin-4-one;
(*R*)-2-(3-(4-Chlorophenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-pyrimidin-4-one;
2-(3-(3-Chlorophenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-pyrimidin-4-one;
2-(3-(2-Chlorophenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-pyrimidin-4-one;
2-(3-(4-Bromophenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-pyrimidin-4-one;
2-(3-(3-Bromophenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-pyrimidin-4-one;
2-(3-(2-Bromophenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-pyrimidin-4-one;
2-(3-(4-Methylphenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-pyrimidin-4-one;
2-(3-(3-Methylphenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-pyrimidin-4-one;
2-(3-(2-Methylphenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-pyrimidin-4-one;
2-(3-(4-Cyanophenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-pyrimidin-4-one;
2-(3-(3-Cyanophenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-pyrimidin-4-one;
2-(3-(2-Cyanophenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-pyrimidin-4-one;
2-(3-(4-Methoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-pyrimidin-4-one;
2-(3-(3-Methoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-pyrimidin-4-one;
2-(3-(2-Methoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-pyrimidin-4-one;
2-(3-(2-Ethoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-pyrimidin-4-one;
2-(3-(5-Fluoro-2-methoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-pyrimidin-4-one;
2-(3-(4-Fluoro-3-methoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-pyrimidin-4-one;
2-(3-(4-Fluoro-2-methoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-pyrimidin-4-one;
(*S*)-2-(3-(4-Fluoro-2-methoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-pyrimidin-4-one;

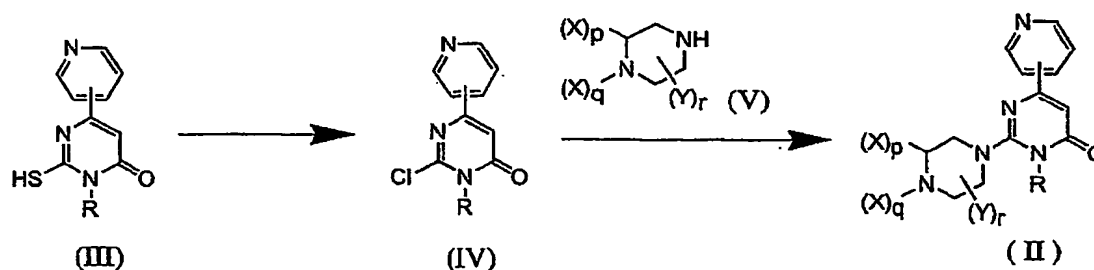
(R)-2-(3-(4-Fluoro-2-methoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
2-(3-(4-Chloro-2-methoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
2-(3-(4-Fluoro-2-methylphenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
2-(3-(2-Fluoro-6-methoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
2-(3-(5-Bromo-2-methoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
2-(3-(2-Bromo-4-fluorophenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
2-(3-(2-Chloro-6-fluorophenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
2-(3-(2,4-Difluorophenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
2-(3-(2,6-Difluorophenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
2-(3-(2,6-Dichlorophenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
2-(3-(2,4-Dimethoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
2-(3-(3,4-Dimethoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
2-(3-(2,5-Dimethoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
2-(3-(2,6-Dimethoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
2-(3-(2,4-Difluoro-6-methoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
2-(3-(5-Cyano-2-methoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
2-(3-(4-Cyano-2-methoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;

2-(3-(1-Naphthyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-pyrimidin-4-one;
2-(3-(2-Naphthyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-pyrimidin-4-one;
2-(3-(2,3-Dihydrobenzofuran-7-yl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-
pyrimidin-4-one;
2-(3-(Benzofuran-2-yl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-pyrimidin-4-one;
(*S*)-2-(3-(Benzofuran-2-yl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-pyrimidin-4-
one;
2-(3-(4-(Pyrrolidin-1-yl-methyl)phenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-
pyrimidin-4-one;
2-(3-(4-(Pyrrolidin-1-yl)phenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-
pyrimidin-4-one;
2-(3-(2-methoxy-4-(pyrrolidin-1-yl)phenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-
3*H*-pyrimidin-4-one;
2-(3-(2-methoxy-5-(pyrrolidin-1-yl)phenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-
3*H*-pyrimidin-4-one;
2-(3-(4-(Phenyl)phenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-pyrimidin-4-one;
2-(3-(4-(4-Fluorophenyl)phenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-
pyrimidin-4-one;
2-(3-(4-(4-Methoxyphenyl)phenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-
pyrimidin-4-one;
2-(3-(4-(2-Methoxyphenyl)phenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-
pyrimidin-4-one;
2-(3-(4-(Morpholin-4-yl)phenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-
pyrimidin-4-one;
2-(3-(4-(4-Methylpiperazin-1-yl)phenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-
pyrimidin-4-one;
2-(4-Phenylpiperazin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-pyrimidin-4-one;
2-(4-Benzylpiperazin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-pyrimidin-4-one;
2-(4-Benzoylpiperazin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-pyrimidin-4-one;
2-(4-(1,2-Benzisothiazol-3-yl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-
pyrimidin-4-one;
2-(4-Methyl-3-phenylpiperazin-1-yl)-3-methyl-6-(4-pyridyl)-3*H*-pyrimidin-4-one;
2-(3-(4-Fluoro-2-methoxyphenyl)-4-methylpiperazin-1-yl)-3-methyl-6-(4-pyridyl)-
3*H*-pyrimidin-4-one;

(S)-2-(3-(4-Fluoro-2-methoxyphenyl)-4-methylpiperazin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
(R)-2-(3-(4-Fluoro-2-methoxyphenyl)-4-methylpiperazin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
2-(4-Acetyl-3-(4-fluoro-2-methoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
2-(4-Benzyl-3-(4-fluoro-2-methoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
2-(4-Benzyl-3-(ethoxycarbonyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
2-(4-methyl-3-(1-naphthyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
2-(5,5-Dimethyl-3-(2-methoxyphenyl)piperazin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
2-(3-Phenylpiperidin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
2-(3-(4-Fluorophenyl)piperidin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
2-(3-(3-Fluorophenyl)piperidin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
2-(3-(2-Fluorophenyl)piperidin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
2-(3-(4-Chlorophenyl)piperidin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
2-(3-(4-Bromophenyl)piperidin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
2-(3-(4-Methoxyphenyl)piperidin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
2-(3-(3-Methoxyphenyl)piperidin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
2-(3-(2-Methoxyphenyl)piperidin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
2-(3-(4-((Pyrrolidin-1-yl)methyl)phenyl)piperidin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
(S)-2-(3-(4-(Pyrrolidin-1-yl-methyl)phenyl)piperidin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one;
(R)-2-(3-(4-(Pyrrolidin-1-yl-methyl)phenyl)piperidin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one; and
2-(3-Hydroxy-3-phenylpiperidin-1-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one.
Salts of the aforementioned preferred compound, and solvates or hydrates of the aforementioned compounds and salts thereof are also preferred.

The 3-substituted-4-pyrimidone compounds represented by the aforementioned formula (I) can be prepared, for example, according to the method

explained below.



(In the above scheme, definitions of R, X and Y are the same as those already described.)

The 2-thiopyrimidinone represented by the above formula (III) is prepared easily by a modification of the method described in EP 354,179. The reaction may be carried out in the presence of a base such as sodium hydroxide, potassium hydroxide, sodium methoxide, sodium ethoxide, potassium tert-butoxide, sodium carbonate, sodium hydrogencarbonate, potassium carbonate, triethylamine, diisopropylethylamine, and 1,8-diazabicyclo[5,4,0]undec-7-en for 1 to 100 hours at a suitable temperature ranging from 0 °C to 200 °C under nitrogen or argon atmosphere or under ordinary air to afford the desired compound (III). Examples of a solvent for the reactions include, for example, alcoholic solvent such as methanol, ethanol, 1-propanol, isopropanol, tert-butanol, ethylene glycol, propylene glycol; etheric solvents such as diethyl ether, tert-butyl methyl ether, tetrahydrofuran, isopropyl ether; hydrocarbonic solvents such as benzene, toluene, xylene; halogenated hydrocarbonic solvents such as dichloromethane, chloroform, dichloroethane; aprotic polar solvents such as formamide, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone, dimethyl sulfoxide, sulfolane, hexamethylphosphoric triamide, water and the like. Generally, a single solvent or a mixture of two or more solvents may be used so as to be suitable to a base used.

Then the 2-thiopyrimidinone derivative (III) is transformed into the 2-chloropyrimidinone (IV) by a chlorinating agent. The reaction time and temperature depend on the chlorinating agent used. Examples of a chlorinating agent for the reactions include, for example, thionyl chloride, thionyl chloride and dimethylformamide, phosphorus oxychloride, phosphorus oxychloride and

dimethylformamide, oxalyl chloride, phosphorous oxychloride and dimethylformamide, and phosphorus pentachloride.

The amine represented by the above formula (V) may be prepared by a modification of the method described in Japanese Patent Unexamined Publication [Kokai] No. 52-139085/1977 or according to well-known methods of one skilled in the art.

Then the chloride derivative (IV) is allowed to react with the amine (V) or salts thereof in the presence of a base such as sodium hydroxide, potassium hydroxide, sodium methoxide, sodium ethoxide, sodium carbonate, sodium hydrogencarbonate, potassium carbonate, triethylamine, diisopropylethylamine, and 1,8-diazabicyclo[5,4,0]undec-7-en for 0.1 to 100 hours at a suitable temperature ranging from 0 °C to 200 °C under nitrogen or argon atmosphere or under ordinary air to afford the desired compound (II).

Examples of a solvent for the reactions include, for example, alcoholic solvent such as methanol, ethanol, 1-propanol, isopropanol, tert-butanol, ethylene glycol, propylene glycol; etheric solvents such as diethyl ether, tert-butyl methyl ether, tetrahydrofuran, isopropyl ether; hydrocarbonic solvents such as benzene, toluene, xylene; halogenated hydrocarbonic solvents such as dichloromethane, chloroform, dichloroethane; aprotic polar solvents such as formamide, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone, dimethyl sulfoxide, sulfolane, hexamethylphosphoric triamide, water and the like. Generally, a single solvent or a mixture of two or more solvents may be used so as to be suitable to a base used.

The compounds of the present invention have inhibitory activity against TPK1, and they inhibit TPK1 activity in neurodegenerative diseases like Alzheimer disease, thereby suppress the neurotoxicity of A β and the formation of PHF and inhibit the nerve cell death. Accordingly, the compounds of the present invention are useful as an active ingredient of a medicament which radically enables preventive and/or therapeutic treatment of Alzheimer disease. In addition, the compounds of the present invention are also useful as an active ingredient of a medicament for preventive and/or therapeutic treatment of ischemic cerebrovascular accidents, Down syndrome, cerebral bleeding due to solitary

cerebral amyloid angiopathy, progressive supranuclear palsy, subacute sclerosing panencephalitis, postencephalitic parkinsonism, pugilistic encephalosis, Guam parkinsonism-dementia complex, Lewy body disease, Pick's disease, corticobasal degeneration frontotemporal dementia, vascular dementia, acute stroke and traumatic injuries, brain and spinal cord trauma, peripheral neuropathies, retinopathies and glaucoma, non-insulin dependent diabetes (such as diabetes type II), and obesity, manic depressive illness, schizophrenia, alopecia, cancers such as breast cancer, non-small cell lung carcinoma, thyroid cancer, T or B-cell leukemia and several virus-induced tumors.

As the active ingredient of the medicament of the present invention, a substance may be used which is selected from the group consisting of the compound represented by the aforementioned formula (I) and pharmacologically acceptable salts thereof, and solvates thereof and hydrates thereof. The substance, per se, may be administered as the medicament of the present invention, however, it is desirable to administer the medicament in a form of a pharmaceutical composition which comprises the aforementioned substance as an active ingredient and one or more of pharmaceutical additives. As the active ingredient of the medicament of the present invention, two or more of the aforementioned substance may be used in combination. The above pharmaceutical composition may be supplemented with an active ingredient of other medicament for the treatment of, for example, Alzheimer disease, vascular dementia, acute stroke and traumatic injuries, brain and spinal cord trauma, peripheral neuropathies, retinopathies and glaucoma, non-insulin dependent diabetes (such as diabetes type II), and obesity, manic depressive illness, schizophrenia, alopecia, cancers such as breast cancer, non-small cell lung carcinoma, thyroid cancer, T or B-cell leukemia and several virus-induced tumors.

A type of the pharmaceutical composition is not particularly limited, and the composition may be provided as any formulation for oral or parenteral administration. For example, the pharmaceutical composition may be formulated, for example, in the form of pharmaceutical compositions for oral administration such as granules, fine granules, powders, hard capsules, soft capsules, syrups, emulsions, suspensions, solutions and the like, or in the form of pharmaceutical compositions for parenteral administrations such as injections for intravenous,

intramuscular, or subcutaneous administration, drip infusions, transdermal preparations, transmucosal preparations, nasal drops, inhalants, suppositories and the like. Injections or drip infusions may be prepared as powdery preparations such as in the form of lyophilized preparations, and may be used by dissolving just before use in an appropriate aqueous medium such as physiological saline. Sustained-release preparations such as those coated with a polymer may be directly administered intracerebrally.

Types of pharmaceutical additives used for the manufacture of the pharmaceutical composition, content ratios of the pharmaceutical additives relative to the active ingredient, and methods for preparing the pharmaceutical composition may be appropriately chosen by those skilled in the art. Inorganic or organic substances, or solid or liquid substances may be used as pharmaceutical additives. Generally, the pharmaceutical additives may be incorporated in a ratio ranging from 1% by weight to 90% by weight based on the weight of an active ingredient.

Examples of excipients used for the preparation of solid pharmaceutical compositions include, for example, lactose, sucrose, starch, talc, cellulose, dextrin, kaolin, calcium carbonate and the like. For the preparation of liquid compositions for oral administration, a conventional inert diluent such as water or a vegetable oil may be used. The liquid composition may contain, in addition to the inert diluent, auxiliaries such as moistening agents, suspension aids, sweeteners, aromatics, colorants, and preservatives. The liquid composition may be filled in capsules made of an absorbable material such as gelatin. Examples of solvents or suspension mediums used for the preparation of compositions for parenteral administration, e.g. injections, suppositories, include water, propylene glycol, polyethylene glycol, benzyl alcohol, ethyl oleate, lecithin and the like. Examples of base materials used for suppositories include, for example, cacao butter, emulsified cacao butter, lauric lipid, witepsol.

Dose and frequency of administration of the medicament of the present invention are not particularly limited, and they may be appropriately chosen depending on conditions such as a purpose of preventive and/or therapeutic treatment, a type of a disease, the body weight or age of a patient, severity of a

disease and the like. Generally, a daily dose for oral administration to an adult may be 0.01 to 1,000 mg (the weight of an active ingredient), and the dose may be administered once a day or several times a day as divided portions, or once in several days. When the medicament is used as an injection, administrations may preferably be performed continuously or intermittently in a daily dose of 0.001 to 100 mg (the weight of an active ingredient) to an adult.

Examples

The present invention will be explained more specifically with reference to examples. However, the scope of the present invention is not limited to the following examples. The compound numbers in the examples correspond to those in the table above.

Reference Example 1: Synthesis of 2-mercapto-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one

A solution of ethyl 3-oxo-3-(4-pyridyl)propionate (29.0 g, 150 mmol), N-methyl thiourea (40.6 g, 450 mmol) and 1,8-diazabicyclo[5,4,0]-7-undecene (22.4 ml, 150 mmol) was refluxed for 4 hours and the solution of methanesulfonic acid (14.4 g, 150 mmol) in water (50 ml) was added after cooling by ice-water. The precipitate was washed with water, filtered and dried to give the title compound (23.7 g, 72%).

$^1\text{H-NMR}$ (DMSO-d_6) δ : 3.58(s, 3H), 6.40(s, 1H), 7.72(dd, $J=1.8, 4.5\text{Hz}$, 2H), 8.73(dd, $J=1.5, 4.8\text{Hz}$, 2H), 12.92(brd, 1H).

Reference Example 2: Synthesis of 2-chloro-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one

Phosphorous oxychloride (26.11g, 170 mmol) was added to dimethylformamide(180 ml) and stirred 20 min. 2-Mercapto-3-methyl-6-(4-pyridyl)-pyrimidine-4-one (24.15 g, 110 mmol) was added to the solution and stirred 5 min and then stirred at 70°C for 2 hours. Ethyl acetate (630 ml) was added to the ice-cooled solution and precipitate was collected by filtration after stirring for 20 minutes. After drying, the precipitate was dissolved in water (400 ml) and pH was

adjusted to 10 by using aqueous sodium hydroxide. The precipitate was washed with water, filtered and dried to give the title compound (18.82 g, 77%).

$^1\text{H-NMR}$ (CDCl_3) δ : 3.72(s, 3H), 6.90(s, 1H), 7.78(dd, $J=1.7, 4.5\text{Hz}$, 2H), 8.75(dd, $J=1.6, 4.5\text{Hz}$, 2H).

Example 1: Synthesis of 2-(2-(4-fluoro-2-methoxyphenyl)piperazin-4-yl)-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one dihydrochloride

A solution of 2-bromo-5-fluoroanisole (11.8 g, 57.6 mmol) in tetrahydrofuran (60 ml) was dropped into the magnesium (1.40 g, 57.6 mmol) in refluxed tetrahydrofuran (32 ml) containing small amount of 1,2-dibromoethane and refluxed for 15 min. After addition of tetrahydrofuran (50 ml), the solution was cooled to -78°C and diethyl oxalate (7.41 g, 50.7 mmol) in diethyl ether (50 ml) was dropped into the solution. After stirring at same temperature for 30 min, the solution was warmed to -10°C and 1N aqueous hydrogen chloride (50 ml) and water were added. Organic layer was extracted with diethyl ether, washed with brine and dried over magnesium sulfate. After removal of the solvent under reduced pressure, purification of the residue by silica gel column chromatography (eluent: hexane/ethyl acetate = 5/2) gave ethyl 2-(4-fluoro-2-methoxyphenyl)-2-oxoacetate (6.80g, 59%)

$^1\text{H-NMR}$ (CDCl_3) δ : 1.40(3H, t, $J=7.1\text{ Hz}$), 3.87(3H, s), 4.89(2H, q, $J=7.1\text{Hz}$), 6.68(1H, d, $J=10.5\text{ Hz}$), 6.77-6.81(1H, m), 7.91-7.95(1H, m).

Ethylenediamine (0.60 g, 10.0 mmol) was added to a solution of ethyl 2-(4-fluoro-2-methoxyphenyl)-2-oxoacetate (2.26 g, 10.0 mmol) in ethanol(30 ml) and refluxed 4 hr. After removal of the solvent under reduced pressure, residue was washed with ethanol-diethyl ether to give 5,6-dihydro-3-(4-fluoro-2-methoxyphenyl)pyrazinone (1.76 g, 79%).

$^1\text{H-NMR}$ (CDCl_3) δ : 3.50-3.56 (2H, m), 3.81 (3H, s), 3.88-3.92 (2H, m), 6.65(1H, d, $J=11.0\text{ Hz}$), 6.70-6.76 (1H, m), 6.89(1H, bs), 7.36-7.40(1H, m).

5,6-Dihydro-3-(4-fluoro-2-methoxyphenyl)pyrazinone was added to the solution of lithium aluminium hydride (0.46 g, 12 mmol) in diethyl ether (25 ml) and refluxed for 6 hr. Water (0.48 ml), 15% sodium hydroxide solution (0.48 ml) and again water (1.21 ml) were added to the ice-cooled solution and the precipitate was

filtered and washed with dichloromethane. Combined organic layer was evaporated to give 2-(4-fluoro-2-methoxyphenyl)piperazine (0.83 g, 99%).

$^1\text{H-NMR}$ (CDCl_3) δ : 2.02(2H, s), 2.57-2.63 (1H, m), 2.80-2.89 (1H, m), 2.92-2.99 (2H, m), 3.06-3.12 (2H, m), 3.80(3H, s), 4.06 (1H, d, $J=10.0$ Hz), 6.56-6.65 (2H, m), 7.40 (1H, t, $J=7.8$ Hz).

2-Chloro-3-methyl-6-(4-pyridyl)-pyrimidin-4-one (222 mg, 1.0 mmol) was added to an ice-cooled solution of 2-(4-fluoro-2-methoxyphenyl)piperazine (210 mg, 1.0 mmol), triethylamine (0.15 ml, 1.1 mmol) in N,N -dimethylformamide (10 ml) and stirred at that temperature for 1 hr and then at room temperature for 2 hr. Next day, reaction was quenched by ice-water and the filtrate was washed with water and dried to give 2-(2-(4-fluoro-2-methoxyphenyl)piperazin-4-yl)-3-methyl-6-(4-pyridyl)-pyrimidin-4-one (246 mg, 62%).

$^1\text{H-NMR}$ (CDCl_3) δ : 2.89-2.96 (1H, m), 3.19-3.31 (3H, m), 3.59 (3H, s), 3.62-3.74 (2H, m), 3.85 (3H, s), 4.39-4.44 (1H, m), 6.63-6.71 (2H, m), 6.67 (1H, s), 7.51-7.55 (1H, m), 7.81 (2H, dd, $J=1.7, 4.6$ Hz), 8.71 (2H, dd, $J=1.7, 4.6$ Hz).

4N Hydrogen chloride in 1,4-dioxane (0.4 ml) was added to the solution of 2-(2-(4-fluoro-2-methoxyphenyl)piperazin-4-yl)-3-methyl-6-(4-pyridyl)-pyrimidin-4-one (217 mg, 0.6 mmol) in dichloromethane (5 ml) and stirred for 15 min. After addition of diethyl ether, filtration and wash with diethyl ether and dryness gave the title compound (260 mg, quant.).

Example 2: Synthesis of 2-(2-(4-methoxyphenyl)piperazine-4-yl)-3-methyl-6-(4-pyridyl)pyrimidin-4-one dihydrochloride

Dimethylsulfoxide (50 ml) solution of 4-methoxyphenacylbromide (9.94 g, 43.4 mmol) and water (1.6 ml, 88.8 mmol) were stirred at 50°C for 2.5 hr. Water was added and the solution was extracted with ethyl acetate 3 times and washed with brine and then dried over sodium sulfate. Removal of the solvent gave 4-methoxyphenylglyoxal (8.30 g, quant.).

$^1\text{H-NMR}$ (DMSO) δ : 3.84 (3H, s), 6.60-6.69 (1H, m), 7.04 (2H, d, $J=8.8$ Hz), 8.05 (2H, d, $J=9.1$ Hz).

Methanol (5 ml) solution of ethylenediamine (3.74 g, 62.29 mmol) was added to the ice-cooled solution of 4-methoxyphenylglyoxal (8.30 g, 45.5 mmol) in

methanol (100 ml) and tetrahydrofuran (50 ml) and stirred for 10 min. After cooling to 0°C, sodium tetrahydroborate (6.14 g, 162.2 mmol) and additional methanol (50 ml) was added and stirred overnight. After removal of the solvent, aqueous sodium hydroxide was added and was extracted with dichloromethane three times and washed with brine and dried over sodium sulfate. After removal of the solvent, purification of the residue by silica gel column chromatography (eluent; dichloromethane/ethanol/diethylamine = 20/2/1) gave 2-(4-methoxyphenyl)-piperazine (3.96 g, 45%).

$^1\text{H-NMR}$ (CDCl_3) δ : 2.69(1H, dd, $J=10.3, 11.9$ Hz), 2.80-3.01(4H, m), 3.07-3.11 (1H, m), 3.68-3.73(1H, m), 3.79(3H, s), 6.84-6.88 (2H, m), 7.27-7.32 (2H, m).

A solution of triethylamine (697 mg, 6.9 mmol), 2-(4-methoxyphenyl)-piperazine (430 mg, tetrahydrofuran (10 ml) was stirred at room temperature for 30 min and at 50°C for 3 hr. Solvent was removed under reduced pressure, and 1N aqueous sodium hydroxide solution was added to the residue and extracted by dichloromethane three times and washed with brine and dried over sodium sulfate. After removal of the solvent under reduced pressure, the residue was purified by silica gel column chromatography (eluent; dichloromethane/ethanol = 10/1) to give 2-(2-(4-methoxyphenyl)-piperazine-4-yl)-3-methyl-6-(4-pyridyl)pyrimidin-4-one (594 mg, 76%)

$^1\text{H-NMR}$ (CDCl_3) δ : 3.02 (1H, dd, $J=10.8, 12.7$ Hz), 3.18-3.25 (3H, m), 3.55 (3H, s), 3.57-3.67 (2H, m), 3.82 (3H, s), 3.98(1H, dd, $J=2.7, 10.8$ Hz), 6.67 (1H, s), 6.92 (2H, d, $J=8.7$ Hz), 7.37 (2H, d, $J=8.7$ Hz), 7.80 (2H, d, $J=6.0$ Hz), 8.71 (2H, d, $J=6.0$ Hz).

4N Hydrogen chloride in ethyl acetate (5 ml) was added to the solution of 2-(2-(4-methoxyphenyl)-piperazine-4-yl)-3-methyl-6-(4-pyridyl)pyrimidin-4-one (594 mg, 1.6 mmol) in dichloromethane (5 ml) and stirred for 1 hr. Wash with ethyl acetate after removal of the solvent and dryness gave the title compound (683 mg, 96%).

Example 3: Synthesis of 2-(2-(4-chlorophenyl)-piperazine-4-yl)-3-methyl-6-(4-pyridyl)pyrimidin-4-one hydrochloride

Mixture of methyl (4-chlorophenyl)acetate (5.10 g, 27.6 mmol) and N-bromosuccinimide (5.16 g, 29 mmol) in carbon tetrachloride was treated by Hg

lamp. After filtration, solvent was removed under reduced pressure and the residue was dissolved in methanol. Ethylenediamine (2.03 ml, 30.4 mmol) and triethylamine (2.06 ml, 14.8 mmol) and di-tert-butyldicarbonate (3.10 ml, 13.5 mmol) were added to the solution of 3-(4-chlorophenyl)piperazin-2-one (2.60 g, 12.3 mmol) in dichloromethane (100 ml) and stirred. The reaction mixture was washed with 1N aqueous hydrogen chloride, water, brine and then dried. After removal of the solvent under reduced pressure, residue was purified by silica gel column chromatography to give 4-(tert-butoxycarbonyl)-3-(4-chlorophenyl)-piperazin-2-one.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.44 (9H, s), 3.21-3.32 (2H, m), 3.48 (1H, m), 4.04 (1H, brs), 5.66 (1H, brs), 7.10 (1H, brs), 7.30-7.38 (4H, m).

Solution of 4-(tert-butoxycarbonyl)-3-(4-chlorophenyl)-piperazin-2-one (500 mg, 1.6 mmol) and acetic acid (929 μl , 16 mmol) were added to a refluxed solution of sodium borohydride (608 mg, 16 mmol) in 1,4-dioxane (5 ml) and reflux was continued. The reaction was quenched by water and extracted with dichloromethane and washed with brine and dried. After removal of the solvent, residue was purified by silica gel column chromatography to give 4-(tert-butoxycarbonyl)-3-(4-chlorophenyl)piperazine (330 mg, 69%).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.46(9H, s), 2.76-2.99(3H, m), 3.13(1H, dd, $J=13.0$ Hz, 4.3 Hz), 3.45-3.49(2H, m), 3.92(1H, m), 5.15(1H, s), 7.27-7.33(4H, m).

A solution of 4-(tert-butoxycarbonyl)-3-(4-chlorophenyl)piperazine (330 mg, 1.1 mmol), 2-chloro-3-methyl-6-(4-pyridyl)pyrimidin-4-one (246 mg, 1.1 mmol) and triethylamine (170 μl , 1.22 mmol) in tetrahydrofuran were refluxed. Usual workup and purification by silica gel column chromatography gave 2-(1-(tert-butoxycarbonyl)-2-(4-chlorophenyl)-piperazine-4-yl)-3-methyl-6-(4-pyridyl)pyrimidin-4-one (500 mg, 93%).

$^1\text{H-NMR}$ (CDCl_3) δ : 1.45(9H, s), 3.09(1H, m), 3.35(3H, s), 3.40-3.63(4H, m), 3.96-4.19(2H, m), 5.43(1H, s), 6.68(1H, s), 7.23(2H, d, $J=8.3$ Hz), 7.32(2H, d, $J=8.3$ Hz), 7.78(2H, d, $J=5.9$ Hz), 8.72(2H, d, $J=5.9$ Hz).

4N Hydrogen chloride in ethyl acetate was added to the solution of 2-(1-(tert-butoxycarbonyl)-2-(4-chlorophenyl)-piperazine-4-yl)-3-methyl-6-(4-pyridyl)pyrimidin-4-one (500 mg, 1.0 mmol) in ethyl acetate and stirred. Filtration

and successive dryness gave the title compound (373mg, 79%).

Example 4: Synthesis of 3-methyl-2-(3-(4-1-pyrrolidinyl)methylphenyl)piperidine-1-yl)-6-(4-pyridyl)pyrimidin-4-one fumarate

Tetrakis(triphenylphosphine)palladium (0.65 g, 0.56 mmol), 4-formylphenylboric acid (2.81 g, 18.7 mmol), 2M aqueous sodium carbonate (18.7 ml, 37.4 mmol) and ethanol were added to the nitrogen-saturated solution of 3-bromopyridine (2.66 g, 16.8 mmol) in toluene and refluxed under nitrogen for 8 hrs. Water was added to the solution and extracted with ethyl acetate, washed with water and brine and dried. Solvents were removed under reduced pressure and the residue was purified by silica gel column chromatography (eluent; hexane/ethyl acetate = 1/1.5) to give 4-(3-pyridyl)benzaldehyde (0.78 g, 25%).

Methyl iodide (0.8 ml, 12.9 mmol) was added to a solution of 4-(3-pyridyl)benzaldehyde (0.78 g, 4.3 mmol) in dichloromethane and stirred 2 days. Additional methyl iodide (0.8 ml, 12.9 mmol) was added and stirred for 3 hr. After removal of the solvent, methanol was added to the residue and ice-cooled. Sodium tetrahydroborate (6.4 g, 17.0 mmol) was added to the solution and stirred for 1.5 hr with warming to room temperature. Organic solvents were removed under reduced pressure after addition of water and extracted with ethyl acetate, washed with water and brine and dried over sodium sulfate. After removal of the solvent under reduced pressure, residue was purified by silica gel chromatography (eluent ethyl acetate to methanol) to give 3-(4-hydroxymethylphenyl)-1-methyl-1,2,5,6-tetrahydropyridine (0.63 g, 72%).

Triethylamine (1.29 ml, 9.2 mmol), acetic anhydride (0.35 ml, 3.7 mmol) were added to a solution of 4-(hydroxymethyl)phenyl-1-methyl-1,2,5,6-tetrahydropyridine (0.63 g, 3.1 mmol) in dichloromethane and stirred overnight. Organic solvents were removed under reduced pressure after addition of water and extracted with ethyl acetate, washed with water and brine and dried over sodium sulfate. Removal of the solvent under reduced pressure gave 3-(4-acetoxymethylphenyl)-1-methyl-1,2,5,6-tetrahydropyridine (0.67 g, 89%).

A solution of 3-(4-acetoxymethylphenyl)-1-methyl-1,2,5,6-tetrahydropyridine (0.67 g, 2.7 mmol) and 1-chloroethyl chloroformate (0.36 ml, 3.3

mmol) in dichloroethane was refluxed for 2 hr. Organic solvents were removed under reduced pressure after addition of water and extracted with ethyl acetate, washed with water and brine and dried over sodium sulfate. After removal of the solvent, methanol was added and refluxed for 1.5 hr. Tetrahydrofuran and water were added to the residue after removal of the solvent under reduced pressure and triethylamine (1.9 ml, 13.6 mmol) and di-tert-butyl dicarbonate (0.66 g, 3.0 mmol) were added and stirred. Organic solvents were removed under reduced pressure after addition of water and extracted with ethyl acetate, washed with water and brine and dried over sodium sulfate. Removal of the solvent under reduced pressure and the residue was purified by silica gel chromatography to give 3-(4-acetoxymethylphenyl)-1-(tert-butoxycarbonyl)-1,2,5,6-tetrahydropyridine (0.71 g, 78%).

Palladium on charcoal was added to the solution of 3-(4-acetoxymethylphenyl)-1-(tert-butoxycarbonyl)-1,2,5,6-tetrahydropyridine (0.71 g, 2.1 mmol) in ethyl acetate and stirred under hydrogen atmosphere. After filtration with celite and removal of the solvent under reduced pressure, methanol and 1N aqueous sodium hydroxide were added and stirred. Organic solvents were removed under reduced pressure after addition of water and extracted with ethyl acetate, washed with water and brine and dried over sodium sulfate. Removal of the solvent under reduced pressure and the residue was purified by silica gel chromatography (eluent; hexane/ethyl acetate = 3/1) to give 3-(4-hydroxymethylphenyl)-1-(tert-butoxycarbonyl)piperidine (0.39 g, 62%).

Triethylamine (0.47 g, 3.4 mmol) and methanesulfonyl chloride (0.12 ml, 1.6 mmol) were added to an ice-cooled solution of 3-(4-hydroxymethylphenyl)-1-(tert-butoxycarbonyl)piperidine (0.39 g, 1.34 mmol) in dichloromethane and stirred for 7.5 hr. Pyrrolidine (1.0 ml, 12 mmol) was added to the solution and stirred overnight. Organic solvents were removed under reduced pressure after addition of water and extracted with ethyl acetate, washed with water and brine and dried over sodium sulfate. Removal of the solvent under reduced pressure and the residue was purified by silica gel chromatography (eluent; ethyl acetate to ethyl acetate/methanol = 1/1, then methanol only) to give 3-(4-(1-pyrrolidinyl)methylphenyl)-1-(tert-butoxycarbonyl)piperidine (0.26 g, 56%).

4N Hydrogen chloride in ethyl acetate was added to 3-(4-(1-pyrrolidiny)-methylphenyl)-1-(tert-butoxycarbonyl)piperidine (0.26 g, 0.75 mmol) and stirred overnight. After filtration and dryness, triethylamine (0.5 ml, 3.6 mmol), 2-chloro-3-methyl-6-(4-pyridyl)-pyrimidin-4-one (0.14 g, 0.63 mmol) and tetrahydrofuran were added and stirred at 70°C. Organic solvents were removed under reduced pressure after addition of water and extracted with ethyl acetate, washed with water and brine and dried over sodium sulfate. Removal of the solvent under reduced pressure and the residue was dissolved into ethyl acetate. A solution of fumaric acid (0.095 g, 0.82 mmol) in acetone was added and the resulting precipitate was filtered and dried to give the title compound (0.29 g, 76%).

Example 5: Synthesis of (R)-2-(2-(4-chlorophenyl)piperazin-4-yl)-3-methyl-6-(4-pyridyl)-pyrimidin-4-one

To a solution of (S)-2-methyl-CBS-oxazaborolidine (27.6 mL, 1.0 M solution in toluene, 27.6 mmol) was added borane-tetrahydrofuran complex (166 ml, 1.0 M solution in tetrahydrofuran, 166 mmol) at -40 °C. To the resulting solution was added a solution of 4'-chlorophenacyl bromide (32.25 g, 138.1 mmol) in tetrahydrofuran (200 ml) through dropping funnel over 1 h at -40 °C. After stirring for 3 hours below 0 °C, methanol (ca. 50 ml) was added dropwise. After stirring the resulting solution for additional 30 min at room temperature, solvent was removed under reduced pressure. The residue, dissolved in ethyl acetate, was treated with 1 N hydrochloric acid to form white precipitate, which was filtered off. The layers of the filtrate was separated, and the organic layer was washed with hydrochloric acid and brine successively, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was used for the next reaction without further purification.

The residue was dissolved in ether (250 ml), and stirred with potassium hydroxide (15.5 g, 276 mmol) in water (250 ml) vigorously. After consumption of the starting material, the layers were separated. The organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was used for the next reaction without further purification.

The residue was heated with benzylamine (37.7 ml, 345 mmol) at 80 °C for 4.5 h. After cooling at room temperature, the resulting white crystals was washed with ether/hexane and collected to afford (S)-2-benzylamino-1-(4-chlorophenyl)-ethanol (23.8 g, 65.8%). The excess benzylamine in the filtrate was distilled off at 120 °C under reduced pressure. From the residue, another (S)-2-benzylamino-1-(4-chlorophenyl)ethanol (2.41 g, 6.7%) was obtained.

^1H NMR (CDCl_3) τ : 2.68(1H, dd, $J=12.3, 8.9\text{Hz}$), 2.92(1H, dd, $J=12.3, 3.7\text{Hz}$), 3.80(1H, d, $J=11.9\text{Hz}$), 3.86(1H, d, $J=11.9\text{Hz}$), 4.68(1H, dd, $J=8.9, 3.7\text{Hz}$), 7.30(9H, m).

To a suspension of (S)-2-benzylamino-1-(4-chlorophenyl)ethanol (15.76 g, 60.21 mmol) and triethylamine (33.6 ml, 241 mmol) in dichloromethane (300 ml) was added a solution of thionyl chloride (4.83 ml, 66.2 mmol) in dichloromethane (20 ml) at -78 °C over 20 min. The resulting suspension was stirred at -78 °C for 20 min and at 0 °C for additional 20 min. The reaction mixture was partitioned between ether and water, and the organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: 10-20% ethyl acetate-hexane) to afford (2RS,5S)-3-benzyl-5-(4-chlorophenyl)-1,2,3-oxathiazolidine 2-oxide (16.2 g 87.4%) as a pale yellow solid.

The resulting product was obtained as a mixture of two diastereomers due to the S-oxide.

major isomer: ^1H NMR (CDCl_3) δ : 3.31(1H, dd, $J=10.5, 9.9\text{Hz}$), 3.55(1H, dd, $J=9.0, 6.3\text{Hz}$), 3.88(1H, d, $J=13.2\text{Hz}$), 4.37(1H, d, $J=13.2\text{Hz}$), 5.49(1H, dd, $J=10.5, 6.3\text{Hz}$), 7.22-7.43(9H, m).

minor isomer: ^1H NMR (CDCl_3) δ : 3.21(1H, dd, $J=13.5, 4.5\text{Hz}$), 3.77(1H, dd, $J=13.5, 11.4\text{Hz}$), 4.05(1H, d, $J=13.5\text{Hz}$), 4.38(1H, d, $J=13.5\text{Hz}$), 5.99(1H, dd, $J=11.4, 4.5\text{Hz}$), 7.22-7.43(9H, m).

A solution of (2RS,5S)-3-benzyl-5-(4-chlorophenyl)-1,2,3-oxathiazolidine 2-oxide (16.2 g, 52.6 mmol) and sodium azide (17.11 g, 263.2 mmol) in N,N-dimethylformamide (100 ml) was heated at 70 °C for 24 hours. The reaction mixture was partitioned between ether and water, and the organic layer was washed with water and brine successively, dried over anhydrous sodium sulfate,

and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: 10-20% ethyl acetate-hexane) to afford (R)-N-benzyl-2-azido-2-(4-chlorophenyl)ethylamine (12.7 g, 83.8%) as a yellow oil. ^1H NMR (CDCl_3) δ : 2.81(1H, dd, $J=12.5, 5.1\text{Hz}$), 2.89(1H, dd, $J=12.5, 8.5\text{Hz}$), 3.82(2H, s), 4.64(1H, dd, $J=8.5, 5.1\text{Hz}$), 7.28-7.36(9H, m).

A solution of (R)-N-benzyl-2-azido-2-(4-chlorophenyl)ethylamine (12.7 g, 44.1 mmol) in tetrahydrofuran (176 mL) was treated with triphenylphosphine (13.9 g, 52.9 mmol) at room temperature. After addition of water (20 ml), the reaction mixture was heated at 60 °C for 1 h. The reaction mixture was condensed, and partitioned between ether and 1 N hydrochloric acid. The aqueous layer was treated with 1 N aqueous sodium hydroxide solution until the solution became basic. The resulting solution was extracted with dichloromethane thoroughly. The combined organic layer was washed with water, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was used for the next reaction without further purification.

The residue was heated with diethyl oxalate (18 ml, 132 mmol) at 120 °C for 1.5 h. The resulting white precipitate was washed with ether and collected to afford (R)-1-benzyl-5-(4-chlorophenyl)-2,3-dioxopiperazine (11.4 g, 82.2%). ^1H NMR (CDCl_3) δ : 3.46(1H, dd, $J=12.9, 8.1\text{Hz}$), 3.60(1H, dd, $J=12.9, 3.8\text{Hz}$), 4.48(1H, d, $J=14.7\text{Hz}$), 4.79(1H, d, $J=14.7\text{Hz}$), 4.80(1H, dd, $J=8.9, 3.8\text{Hz}$), 6.83(1H, s), 7.13(4H, m), 7.27(5H, m).

To a suspension of (R)-1-benzyl-5-(4-chlorophenyl)-2,3-dioxopiperazine (11.4 g, 36.3 mmol) in tetrahydrofuran (300 ml) was added borane-tetrahydrofuran complex (181 mL, 1.0 M solution in tetrahydrofuran, 181 mmol) at room temperature. After stirring for 24 hours, the reaction mixture was quenched with methanol (50 ml) at 0 °C, and concentrated under reduced pressure. The residue was treated with 10% aqueous sodium hydroxide solution (300 ml) and heated at 100 °C for 2 hours. After cooling at room temperature, the mixture was extracted with dichloromethane thoroughly. The combined organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was used for the next reaction without further purification.

To a solution of the residue and triethylamine (7.58 ml, 54.4 mmol) in

dichloromethane (150 ml) was added di-tert-butyl dicarbonate (9.49 g, 43.5 mmol) at room temperature. After stirring for 45 min, the resulting mixture was partitioned between dichloromethane and water, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: 10-20% ethyl acetate-hexane) to afford (R)-1-benzyl-4-(tert-butoxycarbonyl)-3-(4-chlorophenyl)piperazine (11.6 g, 82.8%) as an oil.

^1H NMR (CDCl_3) δ : 1.43(9H, s), 2.16(1H, dt, $J=4.4, 11.7\text{Hz}$), 2.40(1H, dd, $J=4.4, 11.7\text{Hz}$), 2.78(1H, dd, $J=4.4, 11.7\text{Hz}$), 2.98(1H, dt, $J=4.4, 11.7\text{Hz}$), 3.20(1H, d, $J=12.8\text{Hz}$), 3.42(1H, d, $J=12.9\text{Hz}$), 3.57(1H, d, $J=12.9\text{Hz}$), 3.89(1H, d, $J=12.8\text{Hz}$), 5.17(1H, s), 7.24-7.36(9H, m).

To a solution of (R)-1-benzyl-4-(tert-butoxycarbonyl)-3-(4-chlorophenyl)piperazine (11.6 g, 30.1 mmol) in 1,2-dichloroethane (80 ml) was added 1-chloroethyl chloroformate (4.91 ml, 45.1 mmol) at room temperature. Upon disappearance of the starting material, the reaction mixture was concentrated under reduced pressure. The residue was then dissolved in methanol (100 ml) and refluxed for 30 min. The resulting white precipitate was filtered and washed with methanol to afford (R)-2-(4-chlorophenyl)piperazine dihydrochloride, which was liberated with aqueous sodium hydroxide solution, and extracted with dichloromethane to afford (R)-2-(4-chlorophenyl)piperazine (3.04 g, 51.4%) as white solid.

^1H NMR (CDCl_3) δ : 2.65(1H, dd, $J=12.0, 10.5\text{Hz}$), 2.82-3.04(4H, m), 3.09(1H, d, $J=12.6\text{Hz}$), 3.73(1H, dd, $J=10.1, 2.7\text{Hz}$), 7.29(4H, m)

The filtrate was concentrated under reduced pressure and partitioned between ether and 1 N hydrochloric acid. The aqueous layer was neutralized with 1 N aqueous sodium hydroxide solution, and extracted with dichloromethane thoroughly. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified after Boc-protection (Boc_2O , Et_3N , CH_2Cl_2) to furnish (R)-1,4-di(tert-butoxycarbonyl)-2-(4-chlorophenyl)piperazine (2.70 g, 22.6%) as pale yellow solid.

^1H NMR (CDCl_3) δ : 1.43(9H, s), 1.46(9H, s), 2.96(2H, m), 3.32(1H, dd, $J=13.8$,

4.2Hz), 3.74(1H, m), 3.94(1H, d, J=11.4Hz), 4.40(1H, d, J=13.2Hz), 5.23(1H, s), 7.25(2H, m)

To a suspension of (R)-2-(4-chlorophenyl)piperazine dihydrochloride (1.09 g, 4.05 mmol) in tetrahydrofuran (24 ml) was added triethylamine (2.82 ml, 20.3 mmol). After stirring for 15 min at room temperature, 2-chloro-3-methyl-6-(4-pyridyl)-3H-pyrimidin-4-one (748 mg, 3.38 mmol) was added portionwise. Upon disappearance of the chloropyrimidone, the reaction mixture was condensed under reduced pressure. The residue was partitioned between saturated aqueous sodium bicarbonate solution and dichloromethane. The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give pale yellow solid, which was recrystallized from ethanol to afford (R)-2-(2-(4-chlorophenyl)piperazin-4-yl)-3-methyl-6-(4-pyridyl)-pyrimidin-4-one (998 mg, 77.4%) as white crystals. The enantiomer excess was determined by HPLC (>99% ee). The crystals were converted into its dihydrochloride salt.

^1H NMR (DMSO- d_6) δ : 3.40(3H, m), 3.46(3H, s), 3.62(1H, dd, J=12.0, 13.2Hz), 3.72(1H, m), 3.92(1H, t, J=15.5Hz), 4.68(1H, t, J=10.1Hz), 7.18(1H, s), 7.58(2H, d, J=8.6Hz), 7.83(2H, d, J=8.6Hz), 8.57(2H, d, J=6.6Hz), 9.01(2H, d, J=6.6Hz), 10.20(1H, d, J=7.8Hz), 10.76(1H, br s)

MS: 382(M+H)

$[\alpha]_D^{24} = +62.2^\circ$ (c 1.00, H₂O)

Example 6: Synthesis of (S)-2-(2-(4-chlorophenyl)piperazin-4-yl)-3-methyl-6-(4-pyridyl)-pyrimidin-4-one

(S)-isomer was prepared same as above by using (R)-2-methyl-CBS-oxazaborolidine instead of (S)-2-methyl-CBS-oxazaborolidine.

^1H NMR (DMSO- d_6) δ : 3.40 (3H, m), 3.45 (3H, s), 3.53-3.96 (3H, m), 4.68 (1H, t, J = 13.5Hz), 7.10 (1H, s), 7.60 (2H, d, J=8.3Hz), 7.76 (2H, d, J=8.3Hz), 8.38 (1H, br s), 8.91 (1H, d, J=4.8Hz), 9.88 (1H, br s), 10.31 (1H, br s)

MS: 382(M+H)

$[\alpha]_D^{24} = -63.3^\circ$ (c 1.00, H₂O)

The compounds in the following table were prepared in the same manner as

the methods described above. The compound numbers in the following table correspond to those shown in the above-described table of preferred compounds.

Table 3

NO	NMR	Exact-MS
A19	2.51-2.89(4H, m), 3.31-3.34(4H, m), 3.39(3H, s), 3.56(2H, s), 6.80(1H, s), 7.25-7.31(1H, m), 7.31-7.36(4H, m), 7.98(2H, dd, J=1.5, 4.8 Hz), 8.68(2H, dd, J=1.5, 4.5 Hz)(DMSO-d6)	362
A25	3.32-3.34(4H, m), 3.46(3H, s), 3.48-3.51(4H, m), 6.80-6.85(1H, m), 6.84(1H, s), 7.01(2H, d, J=8.0 Hz), 7.23-7.28(2H, m), 8.00(2H, dd, J=1.3, 4.6 Hz), 8.70(2H, dd, J=1.5, 4.5 Hz)(DMSO-d6)	348
A156	3.47(3H, s), 3.51-3.60(4H, m), 3.62-3.71(4H, m), 6.85(1H, s), 7.41-7.49(1H, m), 7.56-7.61(1H, m), 8.02(2H, dd, J=1.5, 4.5 Hz), 8.09(1H, d, J=8.1 Hz), 8.16(1H, d, J=8.1 Hz), 8.70(2H, dd, J=1.5, 4.8 Hz)(DMSO-d6)	405
A289	1.11-1.28(3H, m), 2.98-3.16(1H, m), 3.28-3.41(1H, m), 3.39(3H, s), 3.54-3.80(3H, m), 3.88-3.99(1H, m), 4.08-4.26(4H, m), 4.32-4.45(1H, m), 7.13(1H, s), 7.37-7.53(5H, m), 8.45(2H, d, J=5.8 Hz), 8.96(2H, d, J=6.0 Hz)(DMSO-d6)	434
A361	3.44(3H, s), 3.54-3.95(6H, m), 4.64(1H, brs), 7.11(1H, s), 7.42-7.51(3H, m), 7.74(2H, d, J=6.6 Hz), 8.46(2H, d, J=5.7 Hz), 8.94(2H, d, J=5.7 Hz), 9.98(1H, brs), 10.46(1H, brs)(DMSO-d6)	348
A364	(DMSO-d6): 3.41-3.76(4H, m), 3.48(3H, s), 3.89-4.01(2H, m), 4.96(1H, m), 7.16(1H, s), 7.33-7.58(3H, m), 8.11(1H, dd, J=7.2, 7.2 Hz), 8.52(2H, d, J=6.6 Hz), 8.97(2H, d, J=6.6 Hz), 10.04(1H, m), 10.66(1H, m).	366
A365	3.43(s, 3H), 3.51-3.96(m, 6H), 4.70(m, 1H), 7.00(s, 1H), 7.25(m, 1H), 7.54(m, 2H), 7.60(m, 1H), 8.20(d, J=5.7 Hz, 2H), 8.80(d, J=5.7 Hz, 2H)(CDCl3)	366
A366	2.27-2.85(1H, m), 2.94-3.08(3H, m), 3.43(3H, s), 3.59-3.67(2H, m), 3.94-3.97(1H, m), 6.81(1H, s), 7.19(2H, t, J=8.9 Hz), 7.50-7.55(2H, m), 7.96(2H, dd, J=1.6, 4.5 Hz), 8.68(2H, dd, J=1.5, 4.6 Hz)(DMSO-d6)	366
A366 (HCl)	3.35-3.50(2H, m), 3.46(3H, s), 3.58-3.75(2H, m), 3.86-3.97(2H, m), 4.68(1H, t, J=9.3 Hz), 7.15(1H, s), 7.35(2H, t, J=9.0 Hz), 7.82-7.87(2H, m), 8.48(2H, d, J=6.6 Hz), 8.96(2H, d, J=6.3 Hz), 9.55-10.08(1H, m), 10.54-10.70(1H, m)(DMSO-d6)	366

A369	(CDCl ₃):2.81(1H,dd,J=10.4,12.5Hz), 3.18-3.40(3H,m), 3.50-3.80(5H,m), 4.50(1H,dd,J=2.5,10.1Hz), 6.67(1H,s), 7.20-7.45(3H,m), 7.74(1H,dd,J=1.9,7.6Hz), 7.81(2H,dd,J=1.4,4.6Hz), 8.70(2H,dd,J=1.4,4.6Hz).	382
A370	(CDCl ₃):3.01(1H,dd,J=10.4,12.5Hz), 3.10-3.30(3H,m), 3.50-3.80(5H,m), 4.04(1H,dd,J=2.7,10.8Hz), 6.67(1H,s), 7.20-7.45(4H,m), 7.50(1H,s), 7.80(2H,dd,J=1.5,4.8Hz), 8.71(2H,dd,J=1.5,5.1Hz).	382
A371	3.44(3H,s), 3.44-3.71(7H,m), 3.90(2H,m), 4.66(1H,brs), 7.11(1H,s), 7.55(2H,d,J=8.4Hz), 7.78(2H,d,J=8.4Hz), 8.50(2H,d,J=5.7Hz), 8.95(2H,d,J=5.7Hz), 10.13(1H,brs), 10.60(1H,brs)(DMSO-d ₆)	382
A376	(DMSO-d ₆):3.45(3H,s), 3.50-4.20(6H,m), 4.66(1H,br s), 7.12(1H,s), 7.72(4H,s), 8.44(2H,d,J=6.6Hz), 8.94(2H,d,J=6.6Hz), 10.00(1H,br s), 10.05(1H,br s).	426
A391	3.37-3.93(6H, m), 3.48(3H, s), 3.87(3H, s), 4.89-4.95(1H, m), 7.04-7.12(2H, m), 7.17(1H, d, J=8.5 Hz), 7.45-7.51(1H, m), 7.75-7.81(1H, m), 8.29-8.38(2H, m), 8.83-8.91(2H, m), 9.66-9.77(1H, m), 9.91-10.10(1H, m)(DMSO)	378
A392	(DMSO-d ₆):3.30-3.58(5H,m), 3.58-3.80(2H,m), 3.81(3H,s), 3.85-4.00(2H,m), 4.58-4.75(1H,m), 7.03(1H,dd,J=1.8,8.1Hz), 7.11(1H, s), 7.26(1H,d,J=7.8Hz), 7.35-7.50(2H,m), 8.41(2H,d,J=5.7Hz), 8.92(2H,d,J=6.0Hz), 9.80-10.00(1H,brd), 10.30-10.60(1H,brd).	378
A393	3.40-3.43(5H,m), 3.51-3.63(2H,m), 3.78(3H,s), 3.93(2H,m),4.58(1H,br), 7.02-7.06(3H,m), 7.64(2H,d,J=8.7Hz), 8.34(2H,d,J=6.3Hz), 8.88(2H,d,J=8.7Hz), 9.76(1H,br), 10.16(1H,br)(DMSO-d ₆)	378
A396	1.30(3H, t, J=6.9 Hz), 3.38-3.54(1H, m), 3.49(3H, s), 3.65-3.79(1H, m), 3.84-3.98(2H, m), 4.02-4.18(2H, m), 4.84(1H, t, J=10.5 Hz), 7.04-7.16(2H, m), 7.15(1H, s), 7.39-7.45(1H, m), 7.89(1H, d, J=6.6 Hz), 8.49(2H, d, J=6.3 Hz), 8.95(2H, d, J=6.6 Hz), 9.92(1H, d, J=9.3 Hz), 10.51-10.64(1H, m)(DMSO-d ₆)	392
A406	(DMSO-d ₆):3.64(2H,m), 3.94(2H,t,J=11.4Hz), 4.02-4.40(5H,m), 4.78(1H,t,J=10.4Hz), 7.06(1H,s), 7.98(2H,d,J=8.3Hz), 8.01(2H,d,J=8.3Hz), 8.23(1H,dd,J=1.2,5.1Hz), 9.02(1H,d,J=5.1Hz), 9.31(1H,d,J=1.2Hz), 10.03(1H,d,J=8.7Hz), 10.57(1H,s).	373

A433	(CDCl ₃):2.00(4H,m), 3.03(1H,dd,J=10.8,12.0Hz), 3.21(3H,m), 3.29(4H,m), 3.57(3H,s), 3.62(2H,m), 3.90(1H,dd,J=2.7,10.8Hz), 6.57(2H,d,J=8.7Hz), 6.66(1H,s), 7.29(2H,d,J=8.7Hz), 7.80(2H,d,J=4.8Hz), 8.70(2H,d,J=4.8Hz).	417
A439	(CDCl ₃):3.02(1H,dd,J=10.7,12.4Hz), 3.18(7H,m), 3.55(3H,s), 3.62(2H,m), 3.87(4H,m), 3.96(1H,dd,J=2.5,11.1Hz), 6.66(1H,s), 6.93(2H,d,J=8.7Hz), 7.36(2H,d,J=8.7Hz), 7.79(2H,d,J=4.5Hz), 8.70(2H,d,J=4.5Hz).	434
A442	(CDCl ₃):2.36(3H,s), 2.59(4H,m), 3.02(1H,t,J=11.6Hz), 3.22(7H,m), 3.55(3H,s), 3.63(2H,m), 3.94(1H,d,J=10.5Hz), 6.66(1H,s), 6.93(2H,d,J=8.7Hz), 7.34(2H,d,J=8.7Hz), 7.80(2H,d,J=4.5Hz), 8.70(2H,d,J=4.5Hz).	446
A463	3.41-3.54(3H, m), 3.48(3H, s), 3.69-3.73(1H, m), 3.78(3H, s), 3.82(3H, s), 3.86-3.93(2H, m), 4.89(1H, t, J=10.5 Hz), 6.97-7.01(1H, m), 7.08(1H, d, J=9.0 Hz), 7.15(1H, s), 7.66(1H, d, J=3.0 Hz), 8.51(2H, d, J=6.3 Hz), 8.96(2H, d, J=6.3 Hz), 9.93(1H, d, J=9.0 Hz), 10.60-10.73(1H, m)(DMSO-d ₆)	408
A464	(DMSO-d ₆): 3.45(3H, s), 3.38-3.81(6H, m), 3.88(6H, s), 5.06(1H, m), 6.82(2H, d, J=8.7Hz), 7.04(1H, s), 7.44(1H, t, J=8.4Hz), 8.20(1H, m), 8.30(2H, d, J=6.3Hz), 8.87(2H, d, J=6.3Hz), 10.07(1H, m).	408
A468	3.40-3.50(4H, m), 3.47(3H, s), 3.83-3.94(2H, m), 3.88(3H, s), 4.81-4.91(1H, m), 6.92-6.99(1H, m), 7.07-7.10(1H, m), 7.12(1H, s), 7.79-7.91(1H, m), 8.30-8.40(2H, m), 8.85-8.92(2H, m), 9.70-9.79(1H, m), 10.02-10.23(1H, m)(DMSO)	396
A469/ A470	(DMSO-d ₆):3.38-3.60(6H,m), 3.60-3.80(1H,m) 3.80-4.00(5H,m), 4.80-4.97(1H,m), 6.85-7.00(1H,m), 7.09(1H,dd,J=2.4,11.4Hz), 7.13(1H,s), 7.95(1H,dd,J=6.9,8.7Hz), 8.46(2H,d,J=6.6Hz), 8.94(2H,d,J=6.3Hz), 9.80-10.00(1H,brd), 10.35-10.60(1H,brd).	396
A472	3.36-4.00(6H, m), 3.46(3H, s), 3.94(3H, s), 4.94-5.02(1H, m), 6.96-7.01(1H, m), 7.05(1H, d, J=8.6 Hz), 7.14(1H, s), 7.49-7.58(1H, m), 8.44-8.50(2H, m), 8.52-8.64(1H, m), 8.96(2H, d, J=6.6 Hz), 10.49-10.60(1H, m)(DMSO)	396
A480	2.78(1H, dd, J=10.0, 12.1 Hz), 3.18-3.27(3H, m), 3.59(3H, s), 3.64-3.74(2H, m), 3.86(3H, s), 4.37(1H, dd, J=2.4, 10.1 Hz), 6.67(1H, s), 6.89(1H, d, J=2.1 Hz), 6.99(1H, dd, J=1.7, 8.0 Hz), 7.50(1H, d, J=8.2 Hz), 7.82(2H, dd, J=1.5, 4.8 Hz), 8.71(2H, dd, J=1.8, 4.5 Hz)(CDCl ₃)	412

A490 (2HCl)	3.35-3.94(6H, m), 3.49(3H, s), 4.71-4.80(1H, m), 7.02-7.11(1H, m), 7.18-7.28(2H, m), 7.98-8.10(1H, m), 8.31-8.48(2H, m), 8.87-8.97(2H, m), 9.79-9.92(1H, m), 10.18-10.39(1H, m) (DMSO)	380
A501	(CDCl ₃): 2.77(1H, dd, J=10.2, 12.0Hz), 3.15-3.35(3H, m), 3.50-3.80(5H, m), 3.84(3H, s), 4.39(1H, d, J=7.8Hz), 6.67(1H, s), 6.78(1H, d, J=8.8Hz), 7.39(1H, dd, J=2.4, 8.7Hz), 7.71(1H, d, J=2.3Hz), 7.82(2H, d, J=6.0Hz), 8.71(2H, d, J=6.0Hz).	456
A510	(CDCl ₃): 1.98-2.05(4H, m), 2.85(1H, dd, J=12, 10.5Hz), 3.17-3.24(7H, m), 3.58(3H, s), 3.65-3.72(2H, m), 3.85(3H, s), 4.28(1H, dd, 10.5, 2.7Hz), 6.10(1H, d, J=2.1Hz), 6.18(1H, dd, J=8.7, 2.1Hz), 6.65(1H, s), 7.33(1H, d, J=8.4Hz), 7.83(2H, dd, J=4.5, 1.8Hz), 8.70(2H, dd, J=4.5, 1.5Hz).	447
A511	(CDCl ₃): 1.90-2.05(4H, m), 2.93(1H, t, J=12.0Hz), 3.15-3.40(7H, m), 3.59(3H, s), 3.65-3.85(5H, m), 4.11(1H, dd, J=2.1, 10.2Hz), 6.49(1H, dd, J=3.0, 9.0Hz), 6.66(1H, s), 7.83(2H, dd, J=1.8, 4.5Hz), 8.70(2H, dd, J=1.5, 4.5Hz).	447
A516	(DMSO-d ₆): 3.20-3.70(4H, m), 3.70(1H, m), 3.98(3H, s), 3.99(3H, s), 4.00(1H, m), 4.96(1H, d, J=10.2Hz), 7.01(1H, s), 7.03(2H, m), 8.26(2H, d, J=6.1Hz), 8.53(1H, s), 8.84(2H, d, J=6.1Hz), 10.25(1H, d, J=10.7Hz)	414
A525	(DMSO-d ₆): 3.30-3.50(2H, m), 3.48(3H, s), 3.55-3.78(2H, m), 3.78(3H, s), 3.96(2H, d, J=13.5Hz), 4.69(1H, t, J=10.4Hz), 7.06(1H, t, J=7.4Hz), 7.12(1H, s), 7.14(1H, d, J=7.4Hz), 7.31(1H, d, J=7.4Hz), 7.39(1H, t, J=7.4Hz), 7.59(2H, d, J=8.3Hz), 7.77(2H, d, J=8.3Hz), 8.43(2H, d, J=6.5Hz), 8.93(2H, d, J=6.5Hz), 9.89(1H, d, J=8.7Hz), 10.34(1H, s).	454
A527	(DMSO-d ₆): 3.40-4.10(9H, m), 3.81(3H, s), 4.69(1H, m), 7.05(1H, s), 7.05(2H, d, J=9.0Hz), 7.67(2H, d, J=9.0Hz), 7.75(4H, s), 8.27(2H, d, J=5.7Hz), 8.85(2H, d, J=5.7Hz), 9.75(1H, s), 10.04(1H, s).	454
A536	(DMSO-d ₆): 3.40-3.60(2H, m), 3.47(3H, s), 3.68(2H, m), 3.95(2H, m), 4.71(1H, t, J=9.9Hz), 7.16(1H, s), 7.33(2H, t, J=8.85Hz), 7.78(6H, m), 8.50(2H, d, J=6.3Hz), 8.97(2H, d, J=6.3Hz), 10.02(1H, s), 10.50(1H, s).	443
A543	3.52(s, 3H), 3.57-4.10(m, 6H), 5.57(m, 1H), 7.02(s, 1H), 7.53-7.70(m, 2H), 8.06(d, J=7.2Hz, 2H), 8.21-8.34(m, 3H), 8.82(d, J=6.3Hz, 2H), 9.88-9.92(m, 1H), 10.58-10.61(m, 1H) (DMSO d ₆)	398

A544	3.41-3.59(2H, m), 3.49(3H, s), 3.68-3.76(2H, m), 3.97-4.02(2H, m), 4.78-4.89(1H, m), 7.15(1H, s), 7.58-7.63(2H, m), 7.89-8.07(4H, m), 8.30(1H, s), 8.49(2H, d, J=6.3 Hz), 8.95(2H, d, J=6.3 Hz), 10.17(1H, d, J=8.4 Hz), 10.57-10.70(1H, m)(DMSO-d6)	398
A619	(CDCl ₃): 2.98(1H, dd, J=12.6, 10.8Hz), 3.17-3.28(5H, m), 3.58(3H, s), 3.62(1H, m), 3.79(1H, m), 4.26(1H, dd, 10.5, 2.7Hz), 4.62(2H, m), 6.66(1H, s), 6.88(1H, t, J=7.5Hz), 7.16(1H, d, J=7.2Hz), 7.27(1H, m), 7.84(2H, d, J=6.0), 8.70(2H, dd, J=4.8, 1.2Hz).	390
A626	3.33-3.41(4H, m), 3.42(3H, s), 3.47-3.87(4H, m), 6.84(1H, s), 7.44-7.49(5H, m), 7.99(2H, dd, J=1.5, 4.5 Hz), 8.69(2H, dd, J=1.4, 4.8 Hz)(DMSO-d6)	376
A649	3.44(3H, s), 3.37-4.04(9H, m), 4.67(1H, d, J=9.6Hz), 7.10(1H, s), 7.45-7.55(3H, m), 7.83(2H, d, J=6.0Hz), 8.47(2H, d, J=6.6Hz), 8.95(2H, d, J=6.6Hz), 12.15(1H, brs)(DMSO-d6)	362
A756	(CDCl ₃): 2.50-2.61(1H, m), 2.80-2.95(1H, m), 3.05-3.20(1H, m), 3.25-3.40(1H, m), 3.50-3.60(1H, m), 3.57(3H, s), 3.65-3.75(1H, m), 3.75-3.80(1H, m), 3.85(3H, s), 6.60-6.80(3H, m), 7.47(1H, dd, J=7.2, 8.4Hz), 7.82(2H, dd, J=1.5, 4.5Hz), 8.71(2H, dd, J=1.5, 4.5Hz).	410
A757/ A758	(DMSO-d6): 2.54(3H, s), 3.40-3.79(3H, m), 3.46(3H, s), 3.80-4.10(6H, m), 4.83-5.10(1H, m), 6.90-7.05(1H, m), 7.08(1H, s), 7.13(1H, dd, J=2.7, 11.4Hz), 8.00-8.25(1H, brd), 8.37(2H, d, J=6.3Hz), 8.91(2H, d, J=6.6Hz), 11.80-12.20(1H, brd).	410
A831	2.55(s, 3H), 3.51(s, 3H), 3.67-3.82(m, 4H), 4.04-4.08(m, 2H), 5.64(m, 1H), 7.05(s, 1H), 7.59-7.72(m, 3H), 8.06-8.11(m, 2H), 8.35(d, J=6.6Hz, 2H), 8.41(d, J=7.8Hz, 1H), 8.49(d, J=6.9Hz, 1H), 8.84(d, J=6.6Hz, 2H)(DMSO d6)	412
A1016	(DMSO-d6): 3.15-3.35(1H, m), 3.38-3.60(4H, m), 3.75-4.15(8H, m), 4.18-4.25(1H, m), 4.90-5.20(1H, m), 7.00-7.20(3H, m), 7.30-7.55(6H, m), 8.50-8.70(3H, m), 9.00(2H, d, J=6.3Hz).	486
A1276	(CDCl ₃): 1.80-2.42(3H, m), 3.08-3.39(4H, m), 3.40-3.62(1H, m), 3.65-4.23(6.8H, m), 4.63-4.90(0.6H, m), 5.40-5.62(0.7H, m), 5.80-6.00(0.1H, m), 6.52-6.78(3H, m), 6.90-7.2(1H, m), 7.68-7.90(2H, m), 8.64-8.80(2H, m)	438

A1649	1.48(3H, s), 1.57(3H, s), 3.50(3H, s), 3.51-3.66(2H, m), 3.72-3.76(1H, m), 3.90(3H, s), 3.99(1H, d, J=13.4 Hz), 5.15-5.23(1H, m), 7.08-7.12(2H, m), 7.18(1H, d, J=8.6 Hz), 7.46-7.49(1H, m), 8.04-8.11(1H, m), 8.37-8.45(2H, m), 8.89-8.97(2H, m), 9.49-9.60(1H, m), 9.95-10.11(1H, m)(DMSO)	406
B13	1.16-1.28(1H, m), 1.50-1.64(1H, m), 1.70-1.82(2H, m), 1.90-2.01(1H, m), 2.58(2H, d, J=7.3 Hz), 2.64-2.72(1H, m), 2.89-2.97(1H, m), 3.28(3H, s), 3.57-3.67(2H, m), 6.93(1H, s), 7.20-7.35(5H, m), 8.26(2H, d, J=5.7 Hz), 8.87(2H, d, J=5.9 Hz)(DMSO-d6)	361
B16	1.75-2.16(4H, m), 2.96-3.08(3H, m, 3.55(3H, s), 3.69-3.79(2H, m), 6.66(1H, s), 7.26-7.40(5H, m), 7.81(2H, d, J = 6.0 Hz), 8.70(2H, d, J = 6.0 Hz) (CDCl3)	347
B17	1.76-1.99(5H, m), 2.97-3.10(2H, m), 3.75(1H, d, J=12.4 Hz), 6.81(1H, s), 7.18-7.24(2H, m), 7.28-7.35(1H, m), 7.47(1H, t, J=7.1 Hz), 7.98(2H, d, J=5.8 Hz), 8.68(2H, d, J=5.8 Hz)(DMSO-d6)	365
B19	1.86-2.14(4H, m), 2.94-3.03(3H, m), 3.55(3H, s), 3.68-3.75(2H, m), 6.66(1H, s), 7.05(2H, m), 7.23(2H, m), 7.80(2H, d, J = 6.3 Hz), 8.70(2H, d, J = 6.3 Hz)(CDCl3)	365
B33	1.75-2.08(4H, m), 2.80(1H, m), 3.03(1H, m), 3.42(3H, s), 3.77(2H, m), 3.85(3H, s), 6.65(1H, s), 6.89-7.00(2H, m), 7.22-7.28(2H, m), 7.82(2H, d, J = 6.0 Hz), 8.70(2H, d, J = 6.0 Hz) (CDCl3)	377
B35	1.73-1.83(4H, m), 2.90-3.02(3H, m), 3.42(3H, s), 3.67-3.81(2H, m), 3.74(3H, s), 6.80(1H, s), 6.91(2H, d, J=8.7 Hz), 7.27(2H, d, J=8.5 Hz), 7.97(2H, d, J=5.9 Hz), 8.69(2H, d, J=5.7 Hz)(DMSO-d6)	377
B43	1.69-1.90(7H, m), 1.94-2.00(1H, m), 2.59-2.68(4H, m), 2.92-3.02(3H, m), 3.43(3H, s), 3.69-3.80(4H, m), 6.59(3H, s), 6.79(1H, s), 7.29-7.36(4H, m), 7.96(2H, d, J=5.9 Hz), 8.68(2H, d, J=5.1 Hz)(DMSO-d6)	430
B46	(CDCl3): 1.95-2.09(3H, m), 2.39(1H, m), 3.15(1H, m), 3.45(1H, dd, J=12.9, 10.8Hz), 3.57(3H, s), 3.61-3.72(2H, m), 4.08(1H, m), 6.67(1H, s), 7.32(1H, m), 7.58-7.60(2H, m), 7.74(1H, d, J=7.8Hz), 7.80(2H, dd, J=4.5, 1.5Hz), 8.69(2H, dd, J=4.5, 1.5Hz).	388
B47	(CDCl3): 1.90-2.06(3H, m), 2.36(1H, m), 3.14(1H, m), 3.42(1H, m), 3.57(3H, s), 3.61-3.71(2H, m), 4.06(1H, m), 6.68(1H, s), 7.09(1H, m), 7.28(1H, m), 7.68(1H, dd, J=8.8, 5.1Hz), 7.79(2H, d, J=4.7Hz), 8.69(2H, d, J=5.9Hz).	406

B48	1.90-2.10(3H, m), 2.32-2.44(1H, m), 3.11-3.20(1H, m), 3.45(1H, dd, J=10.5, 12.6 Hz), 3.57(3H, s), 3.61-3.72(2H, m), 4.08(1H, d, J=11.1 Hz), 6.67(1H, s), 7.30-7.35(1H, m), 7.56-7.62(2H, m), 7.74(1H, d, J=13.8 Hz), 7.80(2H, dd, J=1.8, 4.5 Hz), 8.70(2H, dd, J=1.8, 4.8 Hz)(CDCl ₃)	388
B49	1.91-2.09(3H, m), 2.37-2.42(1H, m), 3.12-3.19(1H, m), 3.45(1H, dd, J=10.8, 12.9 Hz), 3.57(3H, s), 3.60-3.72(2H, m), 4.08(1H, d, J=11.1 Hz), 6.67(1H, s), 7.30-7.35(1H, m), 7.54-7.62(2H, m), 7.75(1H, d, J=8.1 Hz), 7.80(2H, dd, J=1.5, 4.5 Hz), 8.70(2H, dd, J=1.8, 4.5 Hz)(CDCl ₃)	388
B50	1.59-1.67(1H, m), 1.72-1.81(1H, m), 2.08(1H, dt, J=3.4, 12.7 Hz), 2.23-2.40(1H, m), 3.06-3.14(1H, m), 3.41-3.54(2H, m), 3.42(3H, s), 3.93(1H, d, J=14.0 Hz), 7.02(1H, s), 7.24-7.29(1H, m), 7.34-7.39(2H, m), 7.56-7.59(2H, m), 8.55(2H, d, J=6.6 Hz), 8.98(2H, d, J=6.5 Hz)(DMSO-d ₆)	363
B80	2.21-2.36(4H, m), 3.19-3.31(2H, m), 3.46(3H, s), 3.88(2H, d, J=13.2 Hz), 6.86(1H, s), 7.38-7.42(1H, m), 7.46-7.51(2H, m), 7.58-7.64(2H, m), 8.01(2H, d, J=5.1 Hz), 8.70(2H, d, J=5.1 Hz)(DMSO-d ₆)	372
B122	1.44(2H, m), 1.75-1.83(3H, m), 2.63(2H, d, J = 6.9 Hz), 2.90(2H, m), 3.51(3H, s), 3.64(2H, m), 6.65(1H, s), 7.17-7.34(5H, m), 7.80(2H, d, J = 6.3 Hz), 8.70(2H, d, J = 6.3 Hz) (CDCl ₃)	361
B123	1.44-2.16(5H, m), 2.86-2.97(2H, m), 3.49(3H, s), 3.62(1H, m), 3.72(1H, m), 4.48(1H, d, J = 7.2 Hz), 6.64(1H, s), 7.07(2H, m), 7.32(2H, m), 7.79(2H, d, J = 6.3 Hz), 8.69(2H, d, J = 6.3 Hz) (CDCl ₃)	395
B124	1.38-1.60(3H, m), 1.78(1H, m), 2.16(1H, m), 2.79-2.94(2H, m), 3.20(3H, s), 3.49(3H, s), 3.59(1H, m), 3.69(1H, m), 3.88(1H, d, J = 7.5 Hz, 1H), 6.64(1H, s), 7.08(2H, m), 7.25(2H, m), 7.79(2H, d, J = 6.0 Hz), 8.70(2H, d, J = 6.0 Hz) (CDCl ₃)	409
B127	1.87-2.06(4H, m), 2.79(1H, m), 3.10(2H, m), 3.57(3H, s), 3.78(2H, m), 6.68(1H, s), 7.23-7.29(3H, m), 7.34(2H, m), 7.84(2H, d, J = 6.0 Hz), 8.72(2H, d, J = 6.0 Hz) (CDCl ₃)	347
B130	1.81-2.03(4H, m), 2.78(1H, m), 3.09(2H, m), 3.57(3H, s), 3.79(2H, m), 6.69(1H, s), 7.03(2H, m), 7.23(2H, m), 7.84(2H, d, J = 5.4 Hz), 8.72(2H, br s) (CDCl ₃)	365
B134	1.78-1.95(4H, m), 2.80-2.91(1H, m), 2.96-3.09(2H, m), 3.45(3H, s), 3.81(2H, d, J=13.1 Hz), 6.80(1H, s), 7.33(1H, dd, J=2.0, 8.3 Hz), 7.56-7.60(2H, m), 7.99(2H, dd, J=1.6, 4.5 Hz), 8.69(2H, dd, J=1.5, 4.5 Hz)(DMSO-d ₆)	415

B145	1.82-2.02(4H, m), 3.09-3.27(3H, m), 3.57(3H, s), 3.79(2H, m), 3.86(3H, s), 6.67(1H, s), 6.89-6.99(2H, m), 7.21-7.26(2H, m), 7.84(2H, d, J = 6.0 Hz), 8.72(2H, d, J = 6.0 Hz) (CDCl ₃)	377
B157	1.85-2.07(2H, m), 2.17-2.30(2H, m), 2.91-3.10(1H, m), 3.10-3.24(2H, m), 3.57(3H, s), 3.71-3.88(2H, m), 6.69(1H, s), 6.99-7.06(1H, m), 7.21(1H, dd, J=2.1, 8.7Hz), 7.45(1H, s), 7.49-7.65(1H, m), 7.83(2H, dd, J=1.8, 4.5Hz), 8.72(2H, dd, J=1.2, 4.8Hz)(CDCl ₃)	405
B158	2.22-2.32(4H, m), 3.22(2H, m), 3.37(1H, m), 3.58(3H, s), 3.82(2H, m), 6.71(1H, s), 7.10(1H, m), 7.29(1H, m), 7.67(1H, m), 7.83(2H, d, J = 6.3 Hz), 8.72(2H, d, J = 6.3 Hz) (CDCl ₃)	406
B159	2.19-2.26(4H, m), 3.21(2H, m), 3.35(1H, m), 3.59(3H, s), 3.82(2H, m), 6.70(1H, s), 6.95(1H, dt, J = 9.0, 2.1 Hz), 7.13(1H, dd, J = 9.0, 2.1 Hz), 7.71(1H, m), 7.85(2H, d, J = 6.3 Hz), 8.72(2H, d, J = 6.3 Hz) (CDCl ₃)	405
B160	2.13-2.34(2H, m), 2.34-2.43(2H, m), 3.10-3.38(3H, m), 3.57(3H, s), 3.68-3.83(2H, m), 6.69(1H, s), 7.29-7.40(2H, m), 7.46-7.59(1H, m), 7.64-7.78(1H, m), 7.80-7.78(2H, m), 8.72(2H, d, J=6.0Hz)(CDCl ₃)	388
B161	2.19(2H, m), 2.38(2H, m), 3.18(2H, m), 3.39(1H, m), 3.58(3H, s), 3.80(2H, m), 6.70(1H, s), 7.39(1H, m), 7.50(1H, m), 7.83(2H, d, J = 6.0 Hz), 7.89(1H, d, J = 7.2 Hz), 8.01(1H, d, J = 7.8 Hz), 8.73(2H, d, J = 6.0 Hz) (CDCl ₃)	404
B162	1.96(2H, m), 2.88(2H, m), 3.15(2H, m), 3.60(3H, s), 3.85(2H, m), 4.63(1H, m), 6.73(1H, s), 7.13-7.23(3H, m), 7.46(1H, d, J = 7.5 Hz), 7.84(2H, d, J = 6.3 Hz), 8.73(2H, d, J = 6.3 Hz)(CDCl ₃)	420
B164	1.64(2H, m), 2.23(2H, m), 3.13(2H, m), 3.50(1H, m), 3.53(3H, s), 3.68(2H, m), 6.58(2H, m), 6.68(1H, s), 6.91(2H, m), 7.81(2H, d, J = 6.0 Hz), 8.72(2H, d, J = 6.0 Hz) (CDCl ₃)	380
B165	1.91-1.99(4H, m), 2.84(3H, s), 3.07(2H, m), 3.55(3H, s), 3.77(2H, m), 3.84(1H, m), 6.69(1H, s), 6.75-6.87(3H, m), 7.27(2H, m), 7.82(2H, d, J = 6.3 Hz), 8.72(2H, d, J = 6.3 Hz) (CDCl ₃)	376
B168	1.52(2H, m), 1.79(3H, s), 1.96(2H, m), 3.09(2H, m), 3.42(3H, s), 3.64(2H, m), 4.86(1H, m), 6.63(1H, s), 7.09-7.19(4H, m), 7.74(2H, d, J = 6.0 Hz), 8.70(2H, d, J = 6.0 Hz) (CDCl ₃)	422
B169	1.86(1H, br s), 1.95(2H, m), 2.30(2H, m), 3.47-3.63(7H, m), 6.68(1H, s), 7.30-7.44(3H, m), 7.54(2H, d, J = 7.5 Hz), 7.84(2H, d, J = 6.0 Hz), 8.71(2H, d, J = 6.0 Hz) (CDCl ₃)	363

B201	2.20-2.31(4H, m), 3.20-3.29(2H, m), 3.46(3H, s), 3.87(2H, d, J=13.8 Hz), 6.86(1H, s), 7.29-7.35(2H, m), 7.64-7.69(2H, m), 8.01(2H, dd, J=1.5, 4.5 Hz), 8.70(2H, dd, J=1.5, 4.5 Hz)(DMSO-d6)	390
B227	2.16-2.25(2H, m), 2.48-2.58(2H, m), 3.14-3.21(2H, m), 3.40(3H, s), 3.41-3.50(2H, m), 6.79(1H, s), 7.28-7.33(1H, m), 7.39-7.46(4H, m), 7.97(2H, dd, J=1.5, 4.5 Hz), 8.68(2H, dd, J=1.5, 4.5 Hz)(DMSO-d6)	389

Test Example: Inhibitory activity of the medicament of the present invention against P-GS1 phosphorylation by bovine cerebral TPK1

A mixture containing 100 mM MES-sodium hydroxide (pH 6.5), 1 mM magnesium acetate, 0.5 mM EGTA, 5 mM β -mercaptoethanol, 0.02% Tween 20, 10% glycerol, 12 μ g/ml P-GS1, 41.7 μ M [γ - 32 P] ATP (68 kBq/ml), bovine cerebral TPK1 and a compound shown in Table (a final mixture contained 1.7% DMSO deriving from a solution of a test compound prepared in the presence of 10% DMSO) was used as a reaction system. The phosphorylation was started by adding ATP, and the reaction was conducted at 25°C for 2 hours, and then stopped by adding 21% perchloric acid on ice cooling. The reaction mixture was centrifuged at 12,000 rpm for 5 minutes and adsorbed on P81 paper (Whatmann), and then the paper was washed four times with 75 mM phosphoric acid, three times with water and once with acetone. The paper was dried, and the residual radioactivity was measured using a liquid scintillation counter. The results are shown in the table below. The test compound markedly inhibited the P-GS1 phosphorylation by TPK1. The results strongly suggest that the medicaments of the present invention inhibit the TPK1 activity, thereby suppress the A β neurotoxicity and the PHF formation, and that the medicaments of the present invention are effective for preventive and/or therapeutic treatment of Alzheimer disease and the above-mentioned diseases.

Table 4

Compound No.	IC ₅₀
A19	0.319 μ M
A25	0.065 μ M
A156	0.140 μ M
A289	2.01 μ M
A361	0.018 μ M
A364	11nM
A365	0.022 μ M
A366	18nM
A366 (HCl)	7.7nM
A369	9.6 nM
A370	5.4 nM
A371	0.0066 μ M
A376	22nM
A391	1.8nM
A392	11nM
A393	0.0047 μ M
A396	25nM
A406	15 nM
A433	21 nM
A439	13 nM
A442	2.0 nM
A463	2.2nM
A464	4.7nM
A468	0.9nM
A469, A470	54nM
A469, A470	0.40nM
A472	5.5nM
A480	0.31 nM
A490(2HCl)	24nM
A501	1.5 nM
A510	2.5nM
A511	3.7 nM
A516	2.0nM
A525	32 nM
A527	5.0 nM
A536	1.6nM
A543	0.0012 μ M
A544	4.6nM

A619	1.6 nM
A626	0.093 μ M
A649	0.855 μ M
A756	56nM
A757, A758	1181nM
A757, A758	34nM
A831	0.015 μ M
A1016	1170 nM
A1276	1674 nM
A1649	7.7nM
B13	0.013 μ M
B16	0.019 μ M
B17	0.0053 μ M
B19	0.024 μ M
B33	0.0027 μ M
B35	0.0075 μ M
B43	0.0013 μ M
B46	0.0018 μ M
B47	0.0088 μ M
B48	0.0098 μ M
B49	0.00078 μ M
B50	0.351 μ M
B80	0.23 μ M
B122	0.052 μ M
B123	0.087 μ M
B124	0.147 μ M
B127	0.026 μ M
B130	0.024 μ M
B134	0.11 μ M
B145	0.033 μ M
B157	0.020 μ M
B158	0.011 μ M
B159	0.0054 μ M
B160	0.0099 μ M
B161	0.0056 μ M
B162	0.015 μ M
B164	0.028 μ M
B165	0.042 μ M
B168	0.041 μ M
B169	0.023 μ M

B201	0.27 μ M
B227	0.062 μ M

Formulation Example

(1) Tablets

The ingredients below were mixed by an ordinary method and compressed by using a conventional apparatus.

Compound of Example 1	30 mg
Crystalline cellulose	60 mg
Corn starch	100 mg
Lactose	200 mg
Magnesium stearate	4 mg

(2) Soft capsules

The ingredients below were mixed by an ordinary method and filled in soft capsules.

Compound of Example 1	30 mg
Olive oil	300 mg
Lecithin	20 mg

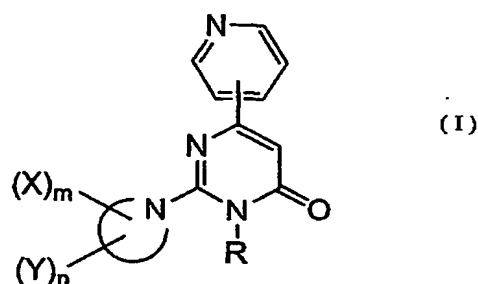
Effect of Invention

The compounds of the present invention have TPK1 inhibitory activity and are useful as an active ingredient of a medicament for preventive and/or therapeutic treatment of diseases caused by abnormal advance of TPK1 such as neurodegenerative diseases (e.g. Alzheimer disease) and the above-mentioned diseases.

【書類名】 外国語要約書

ABSTRACT

A pyrimidone derivative having tau protein kinase 1 inhibitory activity which is represented by formula (I) or a salt thereof, or a solvate thereof or a hydrate thereof:



wherein R represents a C₁-C₁₂ alkyl group; the ring of:



represents piperazine ring or piperidine ring; each X independently represents a C₁-C₈ alkyl group, an optionally partially hydrogenated C₆-C₁₀ aryl ring, an indan ring or the like; m represents an integer of 1 to 3; each Y independently represents a halogen atom, a hydroxy group, a cyano group, a C₁-C₆ alkyl group or the like; n represents an integer of 0 to 8; when X and Y or two Y groups are attached on the same carbon atom, they may combine to each other to form a C₂-C₆ alkylene group.

特願 2 0 0 3 - 1 2 6 0 2 1

出 願 人 履 歴 情 報

識別番号

[0 0 0 0 0 6 7 2 5]

1. 変更年月日

2 0 0 1 年 1 0 月 1 日

[変更理由]

住所変更

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[変更理由] 新規登録

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